STRAINED CARBOCYCLES AS GATEWAYS TO POLYCYCLIC MOLECULAR SCAFFOLDS AND NATURAL PRODUCTS TARGETS

A Dissertation

Presented to

The Academic Faculty

by

Raynold Shenje

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the

School of Chemistry and Biochemistry

Georgia Institute of Technology

August 2016

STRAINED CARBOCYCLES AS GATEWAYS TO POLYCYCLIC MOLECULAR SCAFFOLDS AND NATURAL PRODUCTS TARGETS

Approved by:

Dr. Stefan France, Advisor
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. Seth Marder
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. Adegboyega Oyelere
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. David Collard
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. Christopher Jones
School of Chemical Engineering
Georgia Institute of Technology

Date Approved: May 20th 2016

This thesis is dedicated to my family, specifically my sister Pauline and my brother Lenny. Being big brother to these two has been an incredible influence on my work ethic. I have, throughout my studies, aspired to be an exemplary figure for them and to provide them with a big brother they can be proud of.

Additionally, a most special and sincerest dedication goes to my mother, Sarah. Her unwavering encouragement, fortitude and goodwill ensured my path to the exploration of science and a higher-level education. During all my academic pursuits, I have sought to be the best I can be, not for pride, fame or monetary gain, but solely for the maximization of opportunities granted me by her benevolence. I dedicate these few hundred pages of dissertation as well as my entire contribution to science, past, present, and future, to her.

ACKNOWLEDGEMENTS

Starting from the beginning, I would like to thank St Faith's School, where I obtained high school education. St Faith's fostered an environment of hard-work, perseverance and intellectual competitiveness, attributes that I have found most useful in my academic pursuits. While attending high school I became particularly interested in science and mathematics and for that I thank the enthusiastic and vibrant lectures from Mr. Chigondo, Mr. Makamanzi, and Mr. Madziwa and Mr. Kaitano. Above all others, Mr. Musonza was particularly influential, as he ushered me into the dazzling world of chemistry. His patience, tutelage and high expectations pushed me very close to my limits and up to this day, his mark on my career remains fresh and well-cherished. For that, Mr. Musonza occupies a special place in my life. Along that line, I thank my classmates at St Faith's, some who graduated in 2004 and others in 2006. Many of these gentlemen were highly collaborative and yet intensely competitive, ensuring a healthy environment for academic growth. Ultimately, I thank the leadership of St Faith's High School during my time there, including Mr. Mukoyi, Mr. Mudangwe, and Mr. Mbona among others.

After high school, I began pursuing my Bachelor of Science degree in chemistry at Davidson College. My transition from a Zimbabwean high school to an American college is virtually attributable to a single individual: Rebecca Ziegler Mano. I thank Rebecca for being an exceptional international advisor and assisting me in securing a spot at one of the best colleges in the USA. On the same vein, I would be remiss for not thanking Jackie and Bill Pitzer, who were my host parents throughout college and made a

great impact on my matriculation to the United States. During my time at Davidson College, I benefited immensely from the academic nourishment brought about by being in the presence of true intellectuals. Particularly, I thank Dr. Erland Stevens for fostering my interest in synthetic organic chemistry and allowing me to work as a research fellow under his advisement. I also thank Dr. Striplin, Dr. Nutt and Dr. Brown for their immense help and advice that shaped my young scientific mind. Of course, I thank the institution of Davidson College as a whole whose extreme rigor, academic quality and absolute intellectual integrity I will apprize for the rest of my career.

For my move to Georgia Institute of Technology, I would like to firstly thank Dr. Wendy Kelly for mentoring me during the summer prior to my matriculation. Her guidance and research group were very valuable, and allowed me the advantage to settle in prior to my classmates' arrival to campus. In the first year of my studies, I was mesmerized by the enchanting teachings of Dr. Gelbaum, Dr. Fahrni, Dr. Bredas, Dr. Marder, Dr. France, and Dr. Barlow. These scientists were highly engaging and tremendously knowledgeable which solidified my interest in GA Tech's School of Chemistry and Biochemistry. During the same timespan, I was also a beneficiary of a wonderful set of classmates whose kinship ensured a smooth intellectual transition into graduate school. These colleagues include: Rayaj Ahamed, Karttikay Moudgil, Michelle Razumov-Akbashev, Maitri Desai, and Cynthia Martin among others.

Having solidified my interest in synthetic organic chemistry, I quickly joined the France group. At this time, I would like to express my sincerest gratitude to the main man himself, Dr. Stefan France, for adopting me and taking me under his wing. Joining the France group is one of the best academic decisions I have made to date and I largely

credit Dr. France for it. He has been an incredibly helpful advisor, both in terms fostering and training me when I was new and "green" to challenging me constantly as I became more experienced. Dr. France's apprenticeship model, supervision style, general demeanor, and high expectations benefitted me greatly. I can attest to the fact that I have matured greatly under his tutelage and I thank him for reinforcing in me a hunger for success as well as allowing me the leeway to think independently and experience my own, "self-generated" triumphs and failures. A very inspirational and model mentor indeed!

As an incoming graduate student, I was placed under the tutelage of Dadasaheb Patil, a senior graduate student at the time. Perhaps my most memorable experience in graduate school, working under and being trained by Dadasaheb was a true honor and highly stirring. Dadasaheb was a very capable and intellectually sound graduate student, traits that motivated me as a budding scientist. I thank Dadasaheb for the many conversations we had; they proved useful in helping me navigate graduate school in later years. Other senior students to who helped me grow include: Joel Aponte-Guzman, Marchello Cavitt, Lien Phun, Rebecca Key, and Deepti Sharma. I thank them for their patience and willingness to engage me in my many quandaries, debates and general farcicalities.

Importantly, my humble successes in the lab were, in part, due to my healthy social life outside of it. Along that line, I thank all my friends and acquaintances that helped me relieve stress during my time at Georgia Tech. The include: Rayaj Ahamed, Brian Masunda, Karttikay Moudgil, Cynthia Martin, Rebecca Goudarzi, Umit Kinoglu, Sneha Bishnoi, Maitri Desai, Kunal Desai, Chinmay Kulkarni, Idris Raji, Brett

McLarney, Corey Williams, Manuel Jose Barajas, and Kendez Parker among many others. I was lucky enough to spend time with wonderful people during parties, bar hopping experiences, potlucks, bike rides, road trips etc. I thank them for their much-needed distraction from my studies. I also thank my soccer teammates and anyone I ever had the pleasure of playing soccer with and/or against; soccer was consistently my biggest source of happiness throughout graduate school. Additionally, a special thank you goes to Bethany Martin who has been altruistically supportive throughout my thesis-writing process; she is a true gem.

Finally, I would like to thank my family (Mom – Sarah, Brother – Lenny, Sister – Pauline) for their support and encouragement throughout my academic career. They are the reason I push myself to be the best that I can be. It humbles me to have them by my side.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SYMBOLS AND ABBREVIATIONS

A	Acceptor
ACN	Acetonitrile
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Ad-1-COOH	1-Adamantanecarboxylic acid
Å	Angstrom
$AgSbF_6$	Silver hexafluoroantimonate
AIBN	Azobisisobutyronitrile
$Al(OTf)_3$	Aluminum(III) trifluoromethanesulfonate
AO	Atomic orbital
$AuBr_3$	Gold(III) bromide
β	Beta
$BF_3•Et_2O$	Boron trifluoride diethyl etherate
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
bs	Broad singlet
bt	Broad triplet
n-Bu	n-Butyl
Bu_3SnH	Tributyltin hydride
$Bu_4N(PF_6)$	Tetrabutylammoniumhexafluorophosphate
CaH_2	Calcium hydride
Calc.	Calculated
cat.	Catalytic
$Ca(NTf_2)_2$	Calcium triflimide
^{13}C	Carbon-13
Cbz	Carboxybenzyl
CCl_4	Carbon tetrachloride
$CDCl_3$	Chloroform-d
CDI	1,1'-Carbonyldiimidazole
CF_3COOH	Trifluoroacetic acid
$Co_2(CO)_8$	Dicobalt octacarbonyl
CO	Carbon monoxide
CsOAc	Cesium acetate
CuI	Copper(I) iodide
$Cu(OTf)_2$	Copper(II) triflate
$CuSO_4$	Copper(II) sulfate
δ	Delta or chemical shift
D	Donor
D-A	Donor-acceptor
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
D-A-A	Donor-acceptor-acceptor
D-D-A-A	Donor-donor-acceptor-acceptor
d	Doublet

dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
dtd	Doublet of triplet of doublets
DMAC	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNP	Dinitrophenylhydrazine
dr	Diastereomeric ratio
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
$EtAlCl_2$	Ethylaluminum dichloride
Et_2AlCl	Diethylaluminum chloride
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
F-C	Friedel-Crafts
FMO	Frontier molecular orbital
γ	Gamma
g	Grams
$Ga(OTf)_3$	Gallium(III) trifluoromethanesulfonate
h	Hour
HA	Brønsted acid
^1H	Proton-NMR
H_2	Hydrogen
H_2O_2	Hydrogen peroxide
Hex	Hexane
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
$Hf(OTf)_4$	Hafnium triflate
$Hg(OTf)_2$	Mercury(II) trifluoromethanesulfonate
HRMS	High resolution mass spectrometry
Hz	Hertz
IEDDA	Inverse electron demand Diels-Alder
$InCl_3$	Indium(III) chloride
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
i-Pr	Isopropyl
IR	Infrared spectroscopy
K_2CO_3	Potassium carbonate
$KMnO_4$	Potassium permanganate
LA	Lewis acid
$La(OTf)_3$	Lanthanum(III) triflate
LDA	Lithium diisopropylamide
$LiClO_4$	Lithium perchlorate
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Meta

m	Medium or multiplet
M	Molarity
MeOH	Methanol
$Mg(OTf)_2$	Magnesium triflate
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
mL	Milliliter
MMC	Methyl malonyl chloride
mmol	Millimole
$Mn(OAc)_3$	Manganese(III) acetate
MO	Molecular orbital
MS	Molecular sieves
MsOAc	Methanesulfonyl acetate
N_2	Nitrogen
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NaOAc	Sodium acetate
Na_2SO_4	Sodium sulfate
Naphth	Naphthalene
NEt_3	Triethylamine
$Ni(OTf)_2$	Nickel(II) trifluoromethanesulfonate
NMR	Nuclear magnetic resonance
Nphth	Phthalimido
o	Ortho
O_2	Oxygen
Obs.	Observed
OLED	Organic light-emitting diode
p	Para
PAF	Platelet activating factor
PAA	*p*-Anisaldehyde
Pd	Palladium
Pd/C	Palladium on carbon
$PdCl_2$	Palladium(II) chloride
$Pd(OAc)_2$	Palladium(II) acetate
PFK	Perfluorokerosene
Ph	Phenyl
Pip	Piperdine
PKCβ	Protein kinase Cβ
PMA	Phosphomolybdic acid
$POCl_3$	Phosphoryl trichloride
PPA	Polyphosphoric acid
ppm	Parts-per-million
PQ	Pyrrolo[3,2,1-*ij*]quinoline
Pr	Propyl
$PtCl_2$	Platinum(II) chloride

$PtCl_4$	Platinum(IV) chloride
PtO_2	Platinum(IV) oxide
q	Quartet
qd	Quartet of doublets
qn	Quintet
R_f	Retention factor
Rh_2esp_2	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
$[RhCl_2(Cp^*)]_2]$	Dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer
rt	Room temperature
$Ru_3(CO)_{12}$	Triruthenium dodecacarbonyl
s	Singlet or strong
SAR	Structure-activity relationship
$Sc(OTf)_3$	Scandium(III) triflate
SIRT1	Sirtuin 1
$SnCl_4$	Tin(IV) chloride
t	Triplet
t-Butyl	Tert-butyl
t-BuOOH	Tert-butyl hydroperoxide
td	Triplet of doublets
TBDPS	Tert-butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THI	Tetrahydroindolizine
THQ	Tetrahydroquinoline
$Ti(i\text{-}PrO)_3Cl$	Chlorotitanium triisopropoxide
TIPB	1,3,5-triisopropylbenzene
TLC	Thin-layer chromatography
p-TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
w	weak
$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
$Y(OTf)_3$	Yttrium(III) triflate
ZnI_2	Zinc iodide
$Zn(OTf)_2$	Zinc(II) Triflate

SUMMARY

This PhD. thesis highlights novel uses of strained carbocycles (D-A cyclopropanes and D-A cyclobutanes) in both methodology development and application. At the beginning of each chapter, an exhaustive review of prior approaches to transformations of interest is carried out. The goals of such reviews are primarily three-fold: (1) to discuss to the chosen synthetic phenomena in the proper historical context; (2) to fairly assess these prior synthetic approaches and ascertain their strengths and weaknesses (harshness of reactions conditions, breadth of substrate scope, efficiency, and versatility); and (3) to justify our performed synthetic endeavors as being important additions to the field of interest and to the synthetic community in general.

Highlighted in this thesis are a few novel methodologies pioneered to date. Methods were developed, for the benefit of the synthetic community, to enable access to the following: azepino[1,2-*a*]indoles, cyclohepta[*b*]indoles, functionalized cyclohexenols, hexahydrobenzofurans, and contiguous, tetracyclic heteroaromatic scaffolds. In pursuing these scaffolds, completely new reactivity, was unfolded which included: (1) ring-opening cyclizations of D-A cyclobutanes; and (2) cycloisomerizations of dense, lactone-fused D-A cyclopropanes. Additionally, a strategy for an unprecedented bi-catalytic, tandem continuous flow approach to hydropyrido[1,2-*a*]indoles was successfully forged using "green", scalable, and high-yielding conditions. Throughout this thesis, significant effort was dedicated to widening the accessible chemical space by developing synthetic strategies with particular emphasis on modularity and breath of scope. Presumably, with these methods in hand, synthetic chemists can now apply them, directly, towards the synthesis of select natural products and pharmaceutically-relevant compounds.

CHAPTER 1 INTRODUCTION

1.1 Synthetic Chemistry: Utility and Challenges

For a long time, synthetic chemistry has provided a reliable means to interesting molecules for materials,[1] petrochemical,[2] agrochemical,[3] or pharmaceutical[4] applications. Pharmaceutically-relevant compounds for example, both natural and synthetic, exhibit interesting bioactivities and can often be readily synthesized using judicious synthetic chemistry strategies. The field of the synthetic chemistry thus finds itself invaluable to mankind, and irreplaceable for several reasons: (1) natural products are usually obtained from tedious plant extractions whose yields are often impractically low for large-scale applications; (2) unnatural products, once conjured via genomic and proteomic studies, can only be realized synthetically in the laboratory;[5] (3) the importance of specific (un)natural product functionalities can only be teased out through structure-activity relationships (SARs) via synthetic truncations or elaborations of parent molecules.[6] Due to the power of synthetic chemistry, medicinal chemists are able to take initial (un)natural bioactive hits and fine-tune them into efficacious, value-added compounds enabling a chance at quality therapeutics. This forms the basis of the pharmaceutical industry, and the same principle applies to other chemical industries as well.

The quest for quality compounds for various applications requires sound synthetic strategies as well as robust synthetic methodologies. Much effort has been dedicated to developing methods that allow chemical synthesis with several points of emphasis: (1) efficiency; (2) regioselectivity; (3) chemoselectivity; (4) stereoselectivity; and (5) versatility[7]. It is often very challenging to develop the ideal methodology, encompassing all five mainstays. In addition, society's ever-increasing demand for more sophisticated,

complex, and higher performance molecules is virtually unquenchable. As a result, synthetic chemists are in constant pursuit of robust and improved methodologies to be made available for the entire chemistry community. On the other hand, some chemists pursue concise and elegant syntheses of specific molecular targets of value. Often, the most successful and convincing synthetic chemists combine these two paradigms: the development of novel, in-house methods that are then applied, directly, for targeted synthesis as a demonstration of synthetic utility.

Overall, synthetic organic chemistry has indeed blossomed into an irreplaceably fruitful field of science. Over the past several decades, synthetic chemists have been able to synthesize astoundingly complex compounds (exemplified by taxol[8] and Ciguatoxin CTX3C[9] among many others) as well as effect nearly magical chemical transformations.[10] Even with these awesome accomplishments, synthetic chemistry is yet to reach its pinnacle, and there is still much room for improvement. It has been expressed that new frontiers in synthetic chemistry may lie in rapid, complexity-building reactions and well as one-pot, multistep processes.[7c] Along that line, some criteria that chemists should consider, through research, include: (1) *innovation* – the need to build upon already existing methods, utilizing strategies to make them more robust; (2) *invention* – developing unprecedented transformations, allowing the possibility of new molecular disconnections. In this thesis, the development of new synthetic methods and their applications is highlighted with an emphasis on novelty, efficiency, selectivity, modularity and versatility. Particularly, documented herein are reliable syntheses of medium-sized carbo- and heterocycles, structural motifs that are prominent scaffolds in numerous bioactive compounds.

1.2 Paradigms Within Synthetic Chemistry

While there are numerous approaches to chemical synthesis, the underlying principle remains the same: appropriate starting materials must be transformed into useful intermediates or final products. Early chemists were motivated by the need to elucidate and verify chemical structures and thus used synthetic chemistry as tool towards that end.[11] Since then, the demand to be met by synthetic chemistry has grown to include the need to access bioactive and performance products, structure-activity relationships (SAR), mechanistic probing, as well as showcasing the limits of our synthetic capabilities.[12] In trying to meet this demand, synthetic chemists adopt at least one of three main paradigms of chemical synthesis, depending on the motivation of the synthetic project: (1) target-oriented synthesis; (2) diversity-oriented synthesis; and (3) function-oriented synthesis.

1.2.1 Target-oriented synthesis

Here, the goal is the synthesis of a specific target molecule, chosen using various criteria of bioactivity, physicochemical or electronic properties, structural complexity etc. If the target molecule is a natural product or derivative thereof, this paradigm is commonly referred to as total synthesis and biological activity is usually the drive for synthetic pursuits.[13] In undertaking any target-oriented synthesis, retrosynthesis is a typically employed as tool for making judicious chemical disconnections.[14] Often, the most efficient target-oriented syntheses involve retrosynthetic analyses invoking highly convergent synthetic routes as opposed to linear approaches. Sometimes, a retrosynthetic disconnection features a previously unknown transformation and therefore method development might be undertaken before the full-blown synthesis as validation for the

proposed disconnection. After reasonable retrosynthetic analysis has been proposed, a forward synthesis will then be undertaken. Typically multi-component reactions as well rapid, complexity-forming reactions (such as pericyclic transformations) are employed, allowing for speedy access to the target in a stereoselective manner.[4d, 11a] An example of efficient target-oriented synthesis is the triple domino reaction sequence for accessing the hainanolide and amphilectane frameworks.[15]

1.2.2 Function-oriented synthesis

Natural products with interesting biological activity often possess dauntingly complex molecular structures. At the same time, not all of the structural components of a natural product may be necessary to incite desired bioactivity. Function-oriented synthesis recognizes that the therapeutic value of a molecule can sometimes be realized, if not enhanced, by structurally simpler, easier to synthesize truncations of a complex natural product.[7f] This truncated derivative of a natural product in turn offers the opportunity for further derivatizations that can potentially enhance its biological activity and/or physicochemical properties. In addition, the elimination of unimportant peripheral functionalities in a natural product can have the added benefit of eliminating undesired, off-target activity in biological assays. Function-oriented has successfully be implemented in many instances, for example halichondrin B and dynemicin scenarios, in which their simplified analogs were synthesized in a step economic fashion while maintaining the potency of the original, parent natural products.[16]

1.2.3 Diversity-oriented synthesis

Small molecules can be used as effective probes for biological pathways, facilitating both therapeutic target validation and chemical target validation.[4d, 17]

Considering the general structural intricacy of secondary metabolites, it is generally believed that molecular complexity of small molecules probes is directly proportional to the success of those probes, perhaps due to tighter binding with proteins and enzymes.[4d, 18] The goal of diversity-oriented synthesis is rapid generation of structurally complex small molecules using either reagent-based or substrate-based diversification strategies.[19] These strategies may employ pairings of complexity-building transformations in tandem, alterations of building blocks or utilization of branching reaction pathways.[4d, 20] Chemical diversity and structural complexity can thus be achieved, leading to generation of robust molecular libraries for probing biological systems.

1.3 Natural Products: Utility and Classification

1.3.1 Natural Products as inspiration for therapeutics

The utilization of plant extracts as sources of therapeutic agents dates back thousands of years. Many ancient civilizations, as far back to as 2900 BC, utilized barks, roots, and leaves of plants as remedies for various medical afflictions.[21] As civilization has become more sophisticated, scientists were able to isolate compounds within plant extracts and ascertain their activities against specific diseases. This isolation and characterization led to the concept of "pure compounds" with significantly enhanced efficacies against specific diseases.[21] In the early 19th century, active samples of bioactive agents such as strychnine, atropine, morphine and colchicine were rendered available and ultimately commercialized, with morphine being the first (sold by E. Merck in 1826).[21] Even now, natural products remain a crucial source of effective therapeutics, enabling longer life expectancies and better quality of life.[22]

Nature, through evolution over billions of years, has devised protective mechanisms through a vast array of bioactive natural compounds. These compounds, referred to as secondary metabolites, are produced by plants and microorganisms as protective agents against pests and diseases.[23] The administration of select secondary metabolites remains a mainstay of human-based therapeutics. 61% of anticancer and 49% of anti-infectives over the past several decades have been derived from natural products.[24] The field of natural product discovery identifies potential therapeutics using two main strategies: (1) isolation; and (2) genome mining.[24] Isolation, a traditional discovery technique, involves harvesting plant extracts followed by isolation and characterization of 'hits' in bioactivity assays.[22a] Isolation is often a lengthy process, and is marred by the possibility of missing crucial natural products that may be produced only under specific perturbations. On the other hand, the more recent genome mining strategy involves activation of gene clusters that code for enzymes involved in specific natural products biosynthesis. Genome mining, which invokes genomics, bioinformatics, and genetics, has rejuvenated the field of natural product discovery by offering the ability to realize previously unattainable discoveries.[25] As in the case of coelichelin discovery from *S. coelicolor*, genome mining proves a powerful for predicting the discovery of a previously unknown natural products.[26]

Despite the benefits of natural product discovery towards realization of human therapeutics, the pharmaceutical industry has steadily turned away from this field as a vehicle for drug discovery.[27] This is because of the difficulty in undergoing natural product discovery in a high throughput format and the low percentage of successful discoveries. Current drug discovery efforts in the pharmaceutical industry involve high

throughput screening of molecular libraries to obtain initial 'hits' which are eventually subjected to an extensive lead optimization process to obtain preclinical candidates.[28] As a result, most natural product discovery efforts are limited to academia. However, with the emergence of powerful genome-based techniques, natural product discovery may once again be adopted in the pharmaceutical industry to feed the drug discovery pipeline.

1.3.2 Classes of Natural Products

The total count, structural diversity and bioactivities of nature's secondary metabolites are mind-blowing. More surprisingly, it is likely that many more natural products are yet to be discovered and characterized. The current set of known natural products is subdivided into classes based on structural similarity[29] (Figure 1.1). Structural similarity in natural products results from compounds being synthesized via similar biosynthetic mechanisms. Polyketides, for example, are synthesized from enzymatic condensation of acetate building blocks while terpenes are synthesized from isoprene units.[29b]

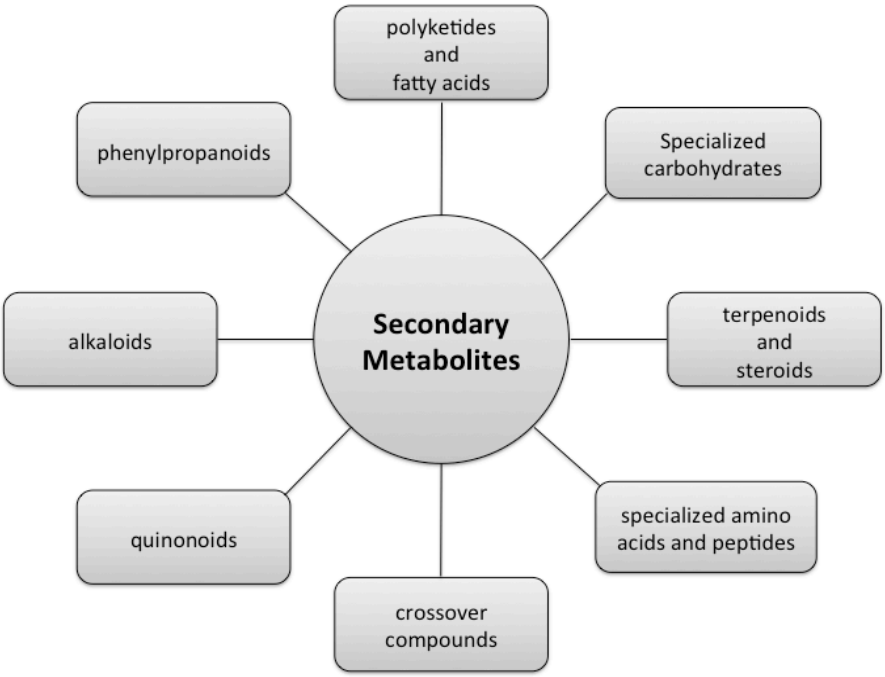


Figure 1.1. Classes of Secondary Metabolites. Crossovers Belong to Multiples Classes.

1.4 Synthetic Strategies Towards Carbo- and Heterocycles

A single glance at any catalog of natural products is enough to realize the importance of rings as structural motifs.[30] Carbo- and heterocycles have thus been of particular interest to synthetic chemists and much effort dedicated towards their synthesis. Approaches to medium-sized ring synthesis include, but are not limited to: (1) metal-mediated cyclizations and annulations;[31] (2) ring-closing metatheses;[32] (3) cycloadditions and electrocyclizations;[33] (4) radical cyclizations;[34] and cascade reactions.[35]

1.4.1 The concept of building blocks for organic synthesis

Despite the synthetic paradigm in which he/she operates (target-oriented, function-oriented or diversity-oriented), a synthetic chemist must take reasonable starting materials and forge them into desired products. Careful consideration and analysis of synthetic routes inevitably leads to the concept of building blocks – synthetic precursors

for the construction of organic compounds.[36] The best and most practical building blocks are easily accessible, cheap and highly versatile. Famous examples include: allenes,[37] alkenes and alkynes,[38] azomethine ylides,[39] diazo compounds,[40] aziridines,[41] and epoxides,[42] aromatic heterocyles[43] etc. Organic building blocks form the basis of the structural architecture of synthetic chemistry.

1.4.2 Strained Carbocycles as Building Blocks for Chemical Synthesis

While there are many useful building blocks for chemical synthesis, cyclopropanes and cyclobutanes are a unique pair carbocycles, offering unparalleled versatility for access to diverse chemical scaffolds. The unique structure and bonding characteristics of these small carbocycles provide the basis for their matchless reactivity. As a result, efforts to understand the reactivity profiles of these building blocks enable their manipulation for strategic effectuation of cutting-edge transformations, an accomplishment beneficial to synthetic chemistry.

1.4.3 Cyclopropane Building Blocks: Background and Bonding

As early as the mid-20th century, chemists recognized the unique and interesting characteristics of cyclopropane. One of these characteristics was the puzzling spectroscopic profile of cyclopropane.[44] When adjoined to double bonds or carbonyls, shifts in the spectra (such as IR) of those systems seemed to indicate some degree of conjugation revealing that cyclopropane had a significant degree of π-character. Further evidence of π-character was later discovered using Raman spectroscopy, whereby a strong similarity between C-H bond of cyclopropane and ethylene was detected.[44] Other studies, such as quenching of cadmium resonance radiation experiments, also pointed towards cyclopropane having π-electrons. In terms of chemical reactivity, cyclopropane

also proved interesting: (1) addition reactions of cyclopropane with Br_2 and H_2 afford 1,2-dibromopropane and propane respectively; (2) conjugate addition-type reactions of ketone-substituted cyclopropanes with nucleophiles; (3) unexpected kinetic stability towards combustion relative to other saturated, low molecular weight hydrocarbons.[45] These unusual properties seemed unique to cyclopropane and rare among any other cycloalkanes. In order to explain the unusual properties and reactivity of cyclopropane, chemists investigated its bonding characteristics. Three main models were invoked: (1) valence-bond (VB) theory; (2) molecular orbital (MO) theory; and (3) σ-aromaticity.

VB theory for cyclopropane, credited to Forster, Coulson and Moffit, depicts the various atomic orbitals involved.[46] In this theory, cyclopropane is constituted of three equivalent C-C bonds and six equivalent C-H bonds. The C-C bond calculated hybridization is $sp^{1.706}$, indicating significant p-character, while that of the C-H bond is $sp^{1.348}$, showcasing relatively high s-character. On the other hand, the overlap integral for C-C bonds is 0.827 and 0.833 for C-H bonds. Typically, higher overlap integral depict more effective mixing of orbitals hence stronger bonds. This data helps explain the unusual strength of cyclopropyl C-H bonds (106.3 kcal/mol vs. 101.1 kcal/mol for ethylene).[47] Another consequence of VB is the phenomenon of "banana" or "bent" bonds (Figure 1.2).[48] In cyclopropane the C-C bonds do not directly point to the carbon centers, and a lot of electron density resides outside the internuclear distance.[49] The bond angle initially starts off at 123° at the carbon atom but decreases with distance; on overage, it is about 110°. "Banana bonds" explain why the effective bond angle in cyclopropane is larger than the mere 60° internuclear angle. Were the bond angles actually 60°, cyclopropane would be expected to have strain energy much higher than 27.7 kcal/mol.

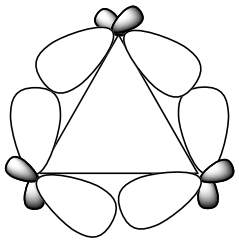


Figure 1.2. "Banana" bonds in Cyclopropane.

The MO theory, also known as the Walsh model, depicts three delocalized occupied molecular orbitals on cyclopropane (Figure 1.3).[44, 50] The lowest-lying MO, housing two electrons, is formed by a linear combination of three sp^2 atomic orbitals and is referred to as the "σ" orbital. The other four electrons reside in two degenerate MOs, known as the "quasi π orbitals" made from linearly combining three p orbitals. These "quasi π orbitals" explain the apparent double bond nature of cyclopropane, both in term of reactivity and spectroscopy.

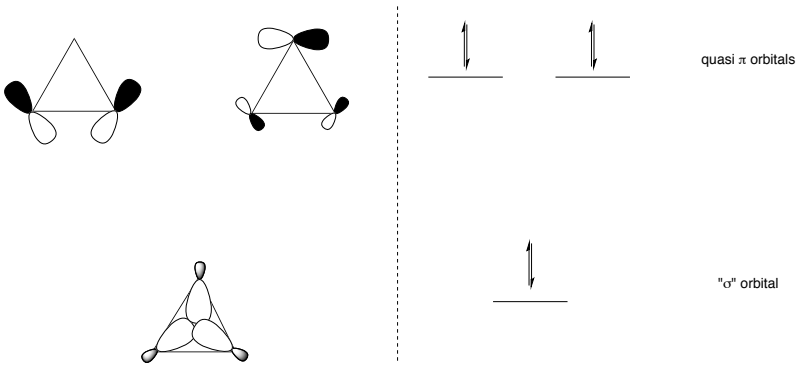


Figure 1.3. Molecular Orbitals of Cyclopropane.

σ-Aromaticity results from not treating σ-bonds as localized entities.[51] In this view, cyclopropane would have a cyclic array of six σ-electrons delocalized over the ring. The cyclopropane C-C bonds would be described as being in "σ-conjugation". As a consequence, invoking the 4n + 2 rule would lead to the conclusion of cyclopropane

being "σ-aromatic".[48] This concept of σ-aromaticity would help explain several interesting phenomena: (1) low strain energy – using vibrational spectroscopy, the strain energy would be estimated to be in the range of 104 kcal/mol, much higher than the experimental value of 27.5 kcal/mol. σ-Aromaticity could justify the unexpected lowering of strain; (2) NMR data – cyclopropane protons are shifted upfield relative to typical values for aliphatic protons. Ring current has been invoked to explain unusual chemical shifts in NMR spectra in many systems.[52] It should be noted, however, that while ring current has become a widely accepted phenomenon, its application to cyclopropane remains controversial as some studies seem to nullify its significance altogether.[53]

1.4.4 Synthesis of Cyclopropanes

As cyclopropanes have become formidable building blocks in synthetic chemistry, a literature survey of general approaches to their synthesis is in order. A variety of robust methods for synthesizing differently substituted cyclopropanes are available. Typically, cyclopropanes are derived from various olefin precursors, which, under the right conditions, undergo predictable reactivity to afford desired cyclopropanes. These conditions include: (1) halomethyl-metal-mediated protocols (Figure 1.4, a); (2) diazo decompositions (Figure 1.4, b); and (3) conjugate addition-cyclizations (Figure 1.4, c and d).[54]

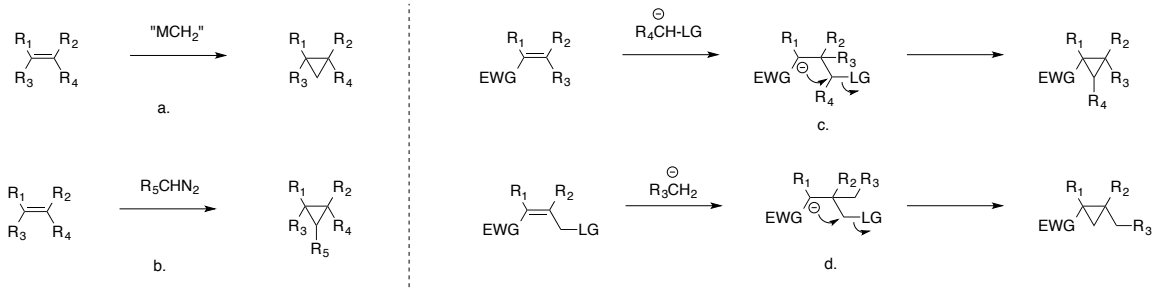
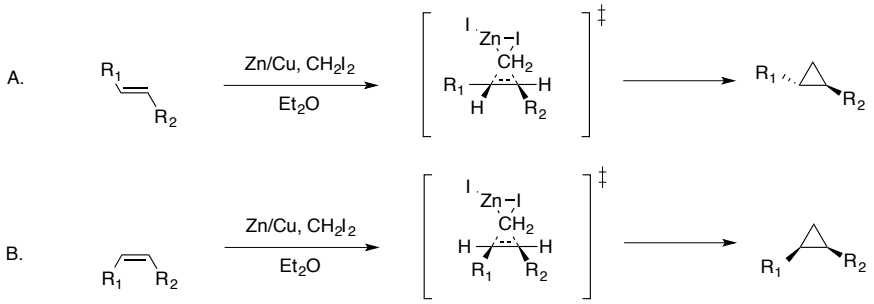


Figure 1.4. Synthetic Routes to Cyclopropane Synthesis.

1.4.4.1 Halomethyl-metal-mediated cyclopropanations

In the presence of diiodomethane, Zn-metal reacts to form an iodomethyl zinc complex, a powerful and stereospecific cyclopropanation agent.[54] Mechanistically, a "butterfly-type" transition state is invoked in describing formation of the cyclopropane concomitant with ZnI_2 generation (Scheme 1.1).[54] As shown, the reaction proceed with complete retention of stereochemistry – *trans*-alkenes produce *trans*-cyclopropanes (Scheme 1.1, A) and vice versa (Scheme 1.1, B). This transformation, also known as the Simmons-Smith reaction, has been used extensively in literature, owing to robustness and excellent chemoselectivity.[55]

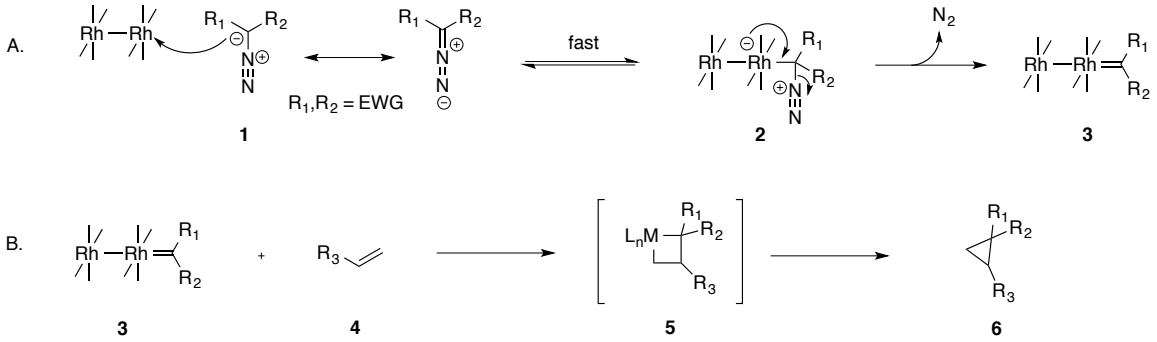


Scheme 1.1. Stereospecific Cyclopropanations via Simmons-Smith Reaction.

1.4.4.2 Cyclopropanations via decomposition of diazo species

Perhaps the most widely used strategy for cyclopropanations, transition metal-catalyzed diazo decompositions in the presence of alkenes are an invaluable tool for

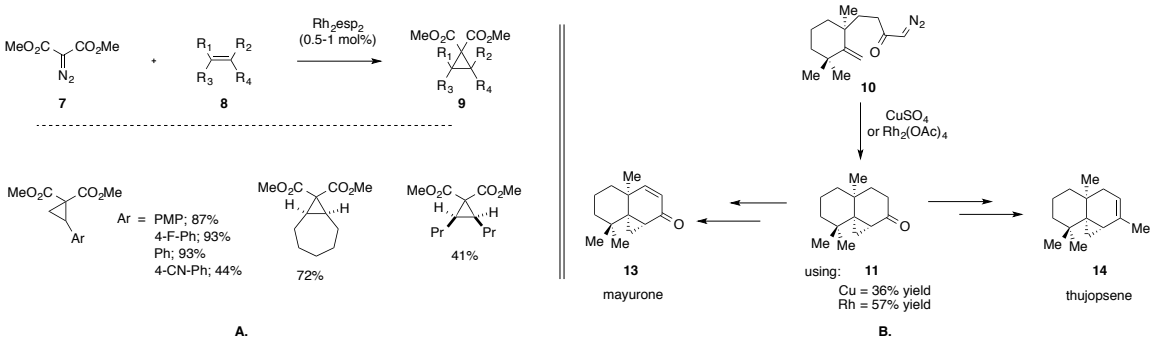
synthetic chemists (Scheme 1.2).[56] Using Rh-based catalysts, for example, the first steps involves a nucleophilic attack of the Rh center by diazo precursor **1** followed by an extrusion of molecular N_2 and Rh(II) carbene **3** formation (Scheme 1.2, A).[57] Once formed, carbenoid **3** can then react with alkene **4** leading to the formation of cyclopropane **6** via metalocyclobutane **5** (Scheme 1.2, B). While the mechanism depicted here is generally applicable for a number of metal-catalyzed cyclopropanations, it is noteworthy that many subtleties exist depending on the choice of metal (Cu, Rh, Ru, Co, Pt etc.), substitutions about the diazo, and electronics of the alkene.[54]



Scheme 1.2. Cyclopropanations via Rhodium Catalysis.

There are various inter- and intramolecular diazo-cyclopropanations available in the literature (Scheme 1.3). For example, malonate diazo **7** undergoes efficient intermolecular, Rh-catalyzed cyclopropanations afford a wide range of cyclopropanes 9 (Scheme 1.3, A).[58] Using this approach, both aromatic and aliphatic alkenes are employed to afford different corresponding cyclopropanes. On the other hand, some innovative intramolecular cyclopropanations using Cu and Rh can be used to access valuable intermediates such **11** (Scheme 1.3, B), which was then used in the total synthesis of mayurone (**13**) and thujopsene (**14**).[59] Additionally, methods for

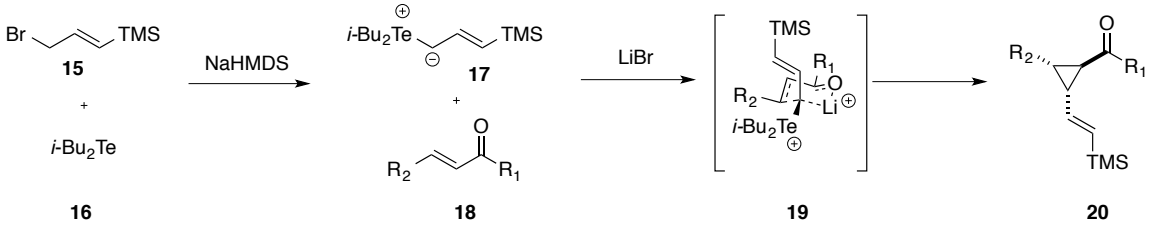
stereoselective cyclopropanations are increasingly being developed through the use of chiral auxiliaries and chiral ligands.[54] Clearly, the versatility of metal-catalyzed diazo-cyclopropanations is invaluable and enables concise synthesis of valuable intermediates and molecular targets.



Scheme 1.3. Cyclopropane Synthesis and Applications in Total Synthesis.

1.4.4.3 Cyclopropanes via conjugate addition-cyclizations

Under basic conditions and in the presence alkyl halides (**15**) diisobutyltellane (**16**) forms tellurium ylides **17**, intermediates that undergo nucleophilic additions onto α,β-unsaturated carbonyl compounds (Scheme 1.4).[54, 60] Following this conjugate addition, a six-membered transition state **19**, facilitated by metal salts, is presumably formed. This transition state features R_1 and R_2 in equatorial positions, leading to their subsequent *trans*-relationship upon cyclopropane formation. The consequential generation of cyclopropane **20** occurs via an intramolecular nucleophilic attack and release of diisobutyltellane (**16**).

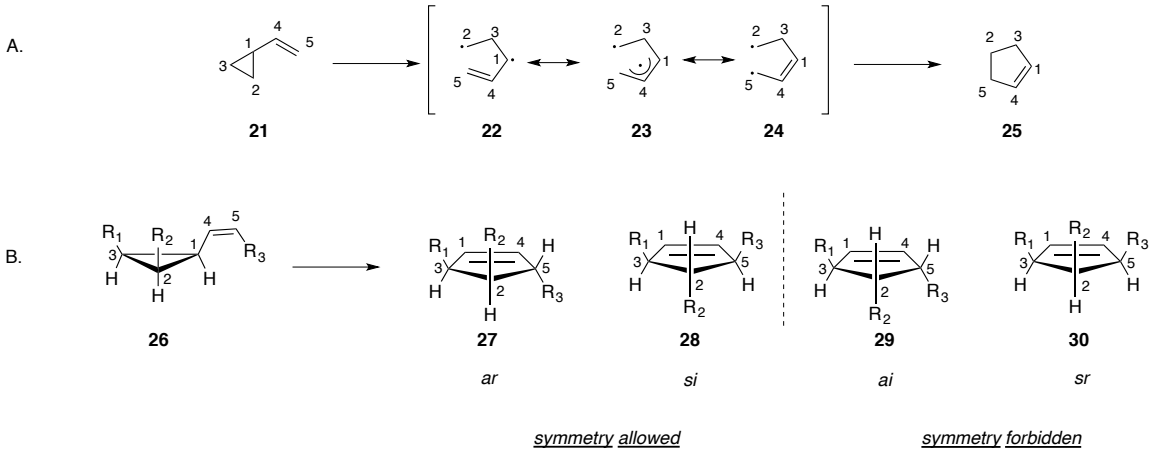


Scheme 1.4. Cyclopropane Synthesis via Conjugate Addition/Nucleophilic Displacement.

1.4.5 Reactivity of cyclopropanes

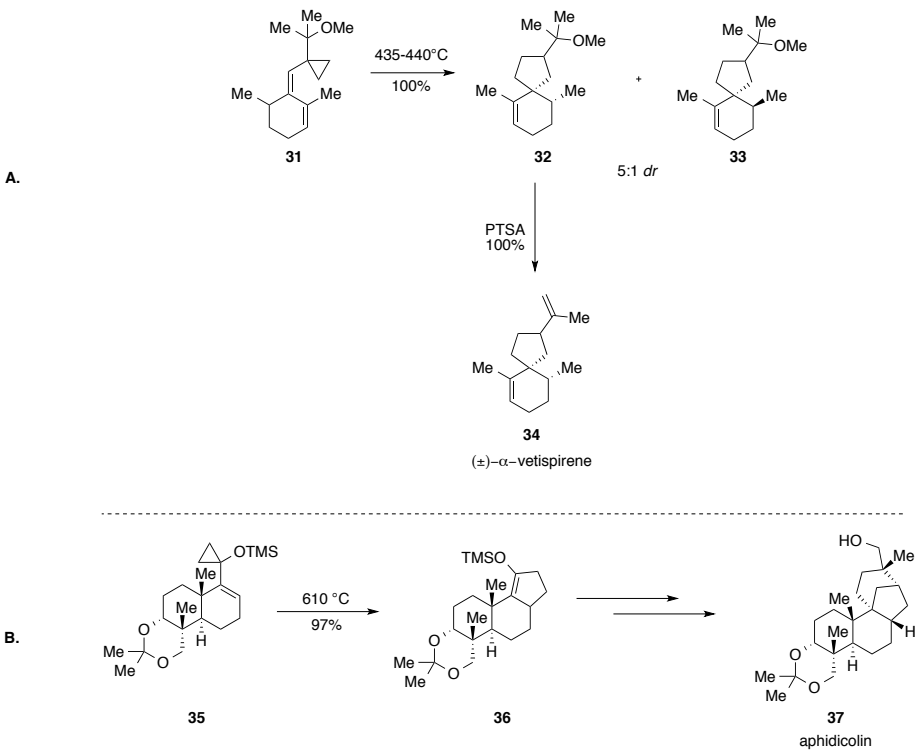
As building blocks, cyclopropanes are famously versatile and undergo a multitude of interesting reactions. Vinylcyclopropane, for example, has garnered much attention in the synthetic community. It was previously discovered that vinylcyclopropane can rearrange, under thermal conditions, to cyclopentene via two plausible mechanistic regimes: (1) diradical pathway; (2) pericyclic pathway.[61] In the diradical pathway, homolytic cleavage of the C(1)-C(2) bond leads to the formation of radical species **24** (Scheme 1.5, A). Cyclization of diradical **24** then leads cyclopentene **25**. As with many transformation involving radical species, the stereochemical outcome of this mechanistic regime tends to unpredictable, and scrambling of stereochemistry is often observed. On the other hand, the pericyclic pathway features a concerted [1,3]-sigmatropic shift and leads to interesting and predictable stereochemical outcomes (Scheme 1.5, B).[61-62] This predictability is because concerted [1,3]-sigmatropic shifts, being pericyclic, are governed by principles of orbital symmetry. Using these considerations, vinylcyclopropane **26** rearrangements can proceed through symmetry allowed antarafacial shift with retention of stereochemistry at C(2) (*ar* pathway). Conversely, a suprafacial pathway with stereochemical inversion at C(2) is also symmetry allowed (*si* pathway). These two symmetry-allowed pathways subsequently lead to cyclopentenes **27** and **28**, respectively. Antarafacial-inversion (*ai*) and suprafacial-retention (*sr*) pathways,

which would afford respective cyclopentenes **29** and **30**, are symmetry forbidden under this regime. It is noteworthy that, sometimes, vinylcyclopropane rearrangements can indeed occur via both the diradical and pericyclic mechanistic regimes in parallel.



Scheme 1.5. Mechanism of Rearrangements of Vinyl Cyclopropane.

Some synthetic chemists have taken advantage of thermal vinylcyclopropane rearrangements for target-oriented synthesis. (±)-(α)-Vetispirene (**34**), for example, has been synthesized via an acid-mediated MeOH elimination on ether **32** (Scheme 1.6, A).[63] Ether **32**, in turn, is derived from a diastereoselective vinylcyclopropane rearrangement of **31** at elevated temperatures. In another example, rearrangement of silylether-substituted cyclopropane **35** affords fused cyclopentene **36**, an important intermediate to the synthesis of HSV-inhibitor aphidicolin **37** (Scheme 1.6, B).[64] While these two examples demonstrate the utility of vinylcyclopropanes in particular, many other cyclopropane derivatives have been employed in effective strategies towards the total synthesis of natural products.[65]

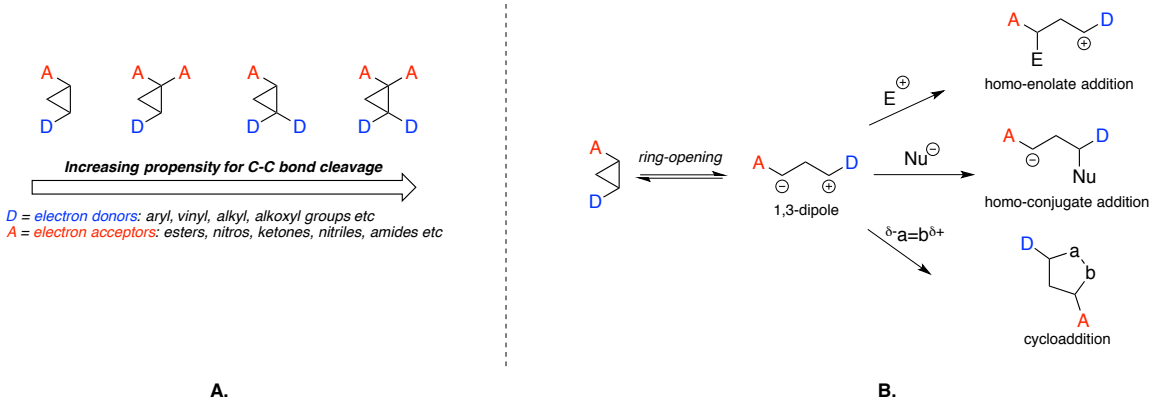


Scheme 1.6. Vinylcyclopropane Rearrangements for Total Syntheses.

1.4.6 Special class of cyclopropanes: D-A cyclopropanes

Within the realm of cyclopropane building blocks is featured an interesting and increasingly popular subclass: the donor-acceptor (D-A) cyclopropanes. Regular, unactivated cyclopropane, while useful via rearrangements and other ring-fission reactions, is kinetically stable thus possesses a significant energy barrier to towards ring-opening. D-A cyclopropanes feature a vicinal donor and acceptor substituents on the cyclopropane. This vicinal substitution polarizes the adjoining C–C bond, allowing for milder heterolytic bond scission (Scheme 1.7, A).[66] Incremental C-C bond polarization has been demonstrated through additional substitutions with donor and acceptor groups on cyclopropane systems. Upon bond cleavage, 1,3-dipoles are formed, intermediates that can undergo a multitude of cyclization,[67] cycloaddition,[68] and nucleophilic addition[69]

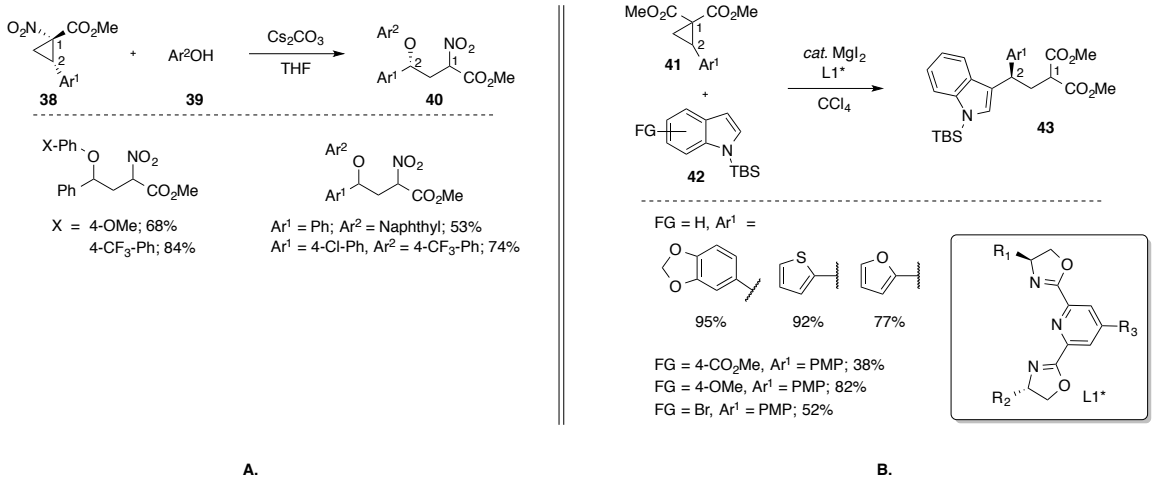
reactions (Scheme 1.7, B). Consequently, D-A cyclopropanes have been utilized as gateways to cyclohexanones, tetrahydropyrans, and fused heteroaromatics, among many other molecular scaffolds.[67d, 70]



Scheme 1.7. Reactivity of Donor-Acceptor Cyclopropanes.

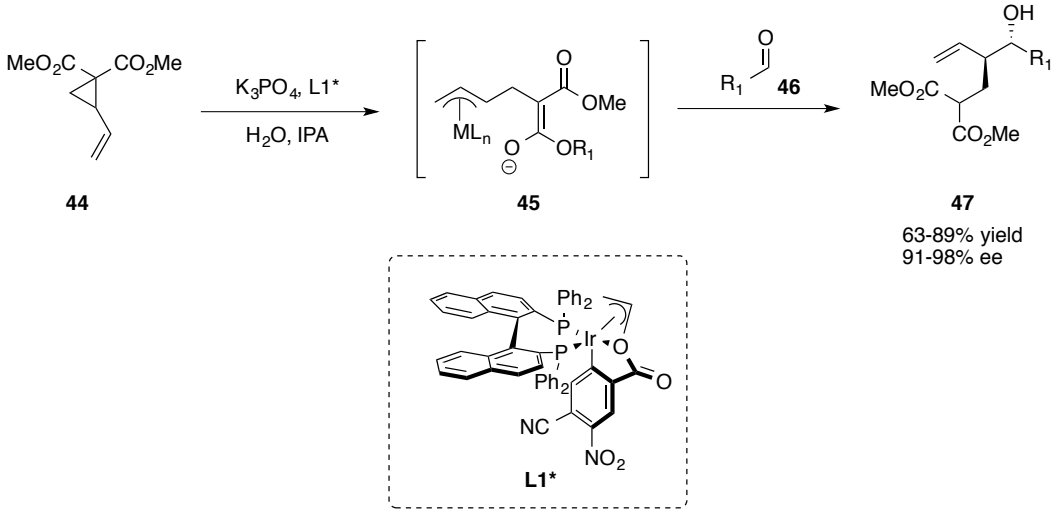
1.4.6.1 D-A Cyclopropanes in Methodology Development

In the presence of aryl alcohols **39** as nucleophiles, D-A cyclopropanes **38** can undergo homo-conjugate addition (Scheme 1.8, A).[71] This transformation, which involves an intermolecular S_N2, attack at C(2), leads to complete inversion of stereochemistry at that center. By utilizing enantio-enriched precursor cyclopropanes, highly enantiopure aryl ethers can be synthesized. Other nucleophilic reactions are also possible with D-A cyclopropanes (Scheme 1.8, B). Arylative homo-conjugate additions, using indoles **42** for instance, have been developed and afford acyclic malonates **43**.[69b] In this example, dynamic kinetic asymmetric transformations (DyKATs) using pybox-type ligands (**L1***), leads to product formation in high ee's.



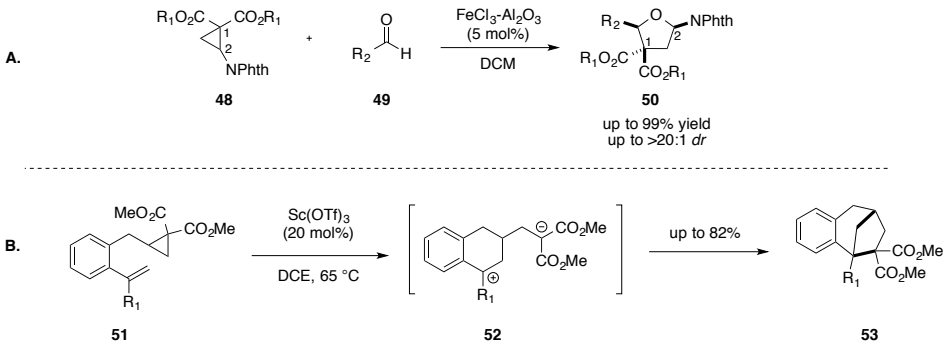
Scheme 1.8. Reactivity of D-A Cyclopropanes with Nucleophiles.

In addition to nucleophiles, electrophiles are also competent reaction partners for D-A cyclopropanes. Along that line, iridium asymmetric catalysis has been applied for the ring opening-reaction of cyclopropane **44** to form a nucleophilic Ir-allyl complex **45** (Scheme 1.9).[72] In the presence of aldehyde electrophiles, an enantioselective C-C coupling occurs to form alcohols **47**. This umpolung approach puts the electrophile next to the donor group and is complementary to normal-polarity cyclopropane reactivity.



Scheme 1.9. Reactivity og D-A Cyclopropanes with Electrophilic Reaction Partners.

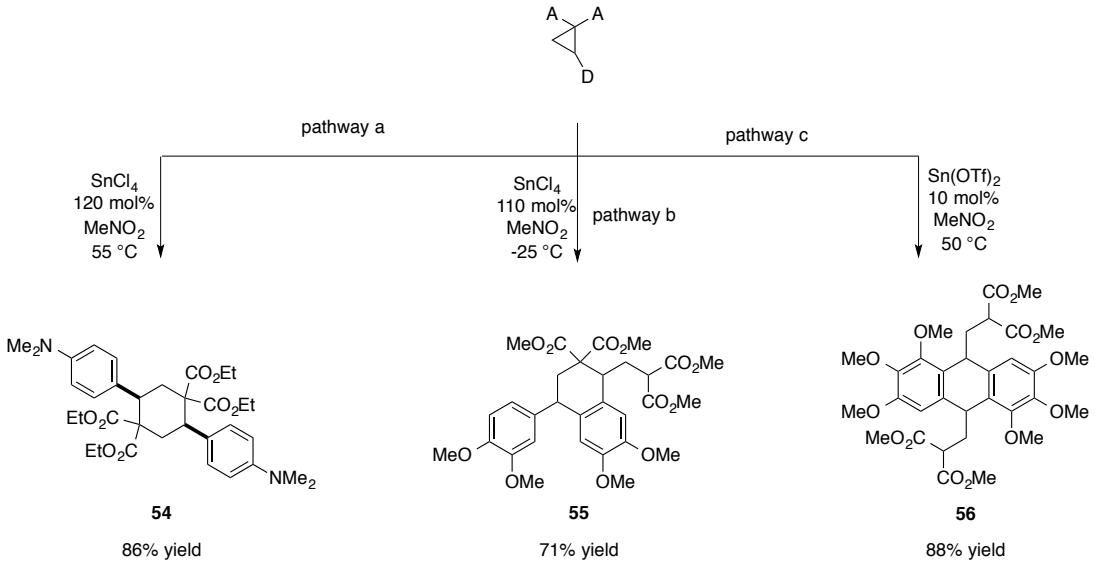
The zwitterion formed upon Lewis acid-catalyzed ring-opening can react with a multitude of dipolarophiles to give [3+*n*]-cycloaddition products. In the presence of aldehydes, for example, functionalized tetrahydrofurans **50** are easily accessed using catalytic Fe conditions via an intermolecular [3+2]-cycloaddition transformation (Scheme 1.10, A).[73] Other interesting variations utilize intramolecular pathways as a means to access bicyclic scaffolds (Scheme 1.10, B). The tethered D-A cyclopropane **51** undergoes a Sc-catalyzed ring-opening cyclization to afford 1,5-dipole **52**. Subsequent cyclization of dipole **52** leads to bicyclo[3.2.1]octanes **53**.[74] The net transformation is an intramolecular [3+2]-cycloaddition. The scope of possible intra- and intermolecular [3+2]-cycloadditions possible using D-A is vast: many tetrahydrofurans,[75] pyrrolidines,[76] acetal[*n*.2.1] frameworks,[77] cyclopenta[*c*]chromenes,[78] indene-2,4-diones,[79] pyrrolo-isoxazolidines,[80] among many other fused-ring systems,[81] are thus prepared this way.



Scheme 1.10. [3+2]-Cycloaddition Reactions of D-A Cyclopropanes.

Using D-A cyclopropanes with highly electron-rich donor groups, [3+3]-cyclodimerizations are possible (Scheme 1.11).[82] These transformations are characteristically sensitive to reaction conditions including solvent, temperature, donor substitutions patterns, and Lewis acid promoters. Strong Lewis acids, such as $SnCl_4$,

typically promote cyclodimerization (pathways a and b), leading to the formation of 1,4-diarylated cyclohexanes **54** and tetrahydronaphthalenes **55**, respectively. Product **54** is formed from a head-tail-type dimerization of one zwitterion onto the other, while **55** results from an intramolecular Friedel-Crafts alkylation one dimer segment by the donor of another. Finally, cyclodimerization pathway c, which involves no participation of the enolates formed, occurs via carbocation trappings of the donor-stabilized carbocations of each donor by the donor group of the other. This pathway affords dihydroanthracenes **56** and is catalyzed by the relatively less Lewis acidic $Sn(OTf)_2$ catalyst. For each pathway, judicious substitutions on the donor groups allow tunability towards the intramolecular attack of the intermediate carbocations with either enolate of aryl group.



54
86% yield

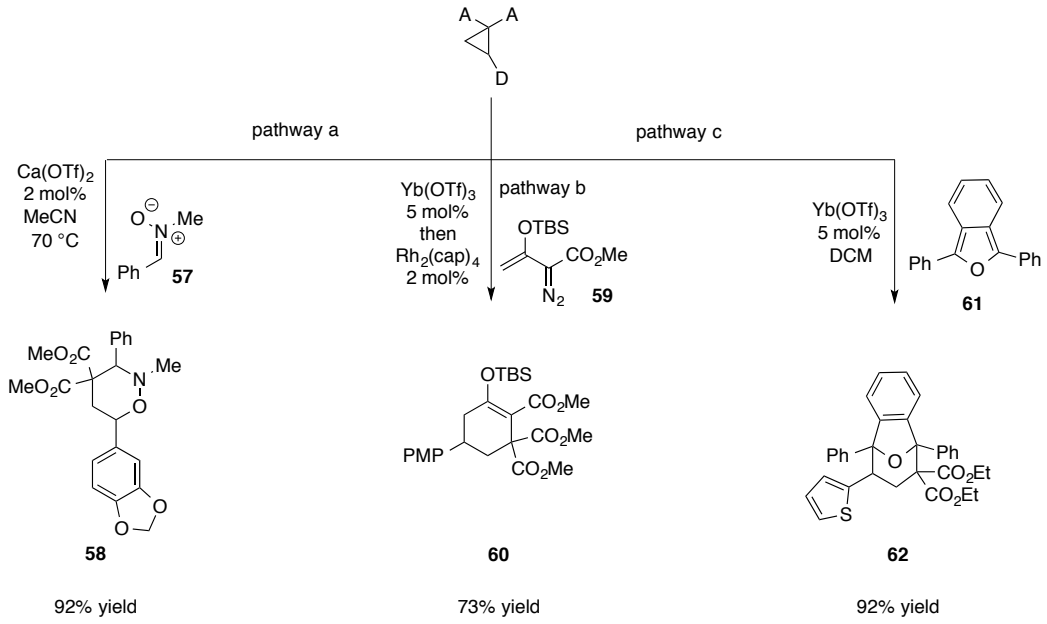
55
71% yield

56
88% yield

Scheme 1.11. [3+3]-Cyclodimerization Reactions of D-A Cyclopropanes.

Many other [3+*n*]-cycloadditions are available (Scheme 1.12) using D-A cyclobutanes and nitrones, azides, dienes and other cycloaddition coupling partners.[83] Some interesting examples include [3+3]-cycloadditions with nitrones **57** and α-diazos **59** to form highly functionalized 1,2-oxazines **58**[84] and cyclohexene **60**,[85] respectively.

Cyclohexene **60** formation involves an initial [3+2]-cycloaddition of a D-A cyclopropane with silyl enol ether **59**, followed by a Rh-catalyzed ring-expansion; the result being a formal [3+3]-cycloaddition. On the other hand, in the presence of 1,2-diphenylisobenzofuran (**61**) and $Yb(OTf)_3$-catalyzed, D-A cyclopropanes can under [3+4] cycloadditions to form dense polycycle **62** in 92% yield.[86]

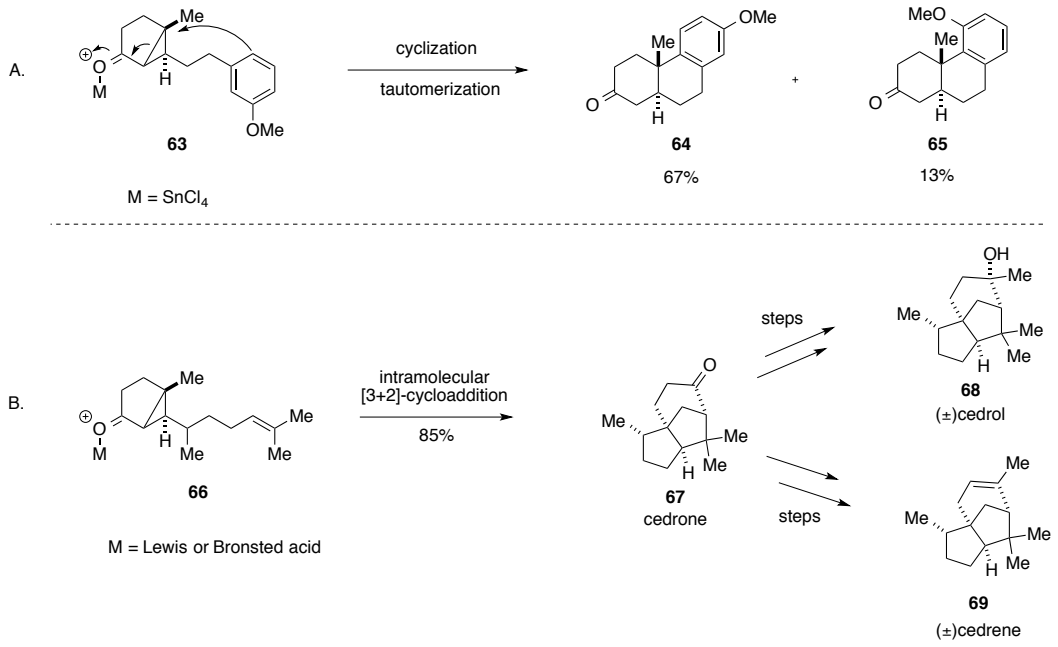


Scheme 1.12. Other [3+n]-Cycloadditions of D-A Cyclopropanes.

1.4.6.2 D-A Cyclopropanes in Total Synthesis of Natural Products

As has been highlighted, D-A cyclopropanes are highly versatile building blocks and allow synthesis of many interesting chemical motifs. Importantly, the synthetic utility of D-A cyclopropanes has been further demonstrated through their use in the total synthesis of natural products. More than forty years ago, Stork et. al. reported a novel D-A cyclopropane ring-opening cyclization for the assembly of interesting fused polycycles **64** and **65** (Scheme 1.13, A).[87] Corey et al. then adopted this method in the total synthesis of (±)-cedrene (**69**) and (±)-cedrol (**68**) (Scheme 1.13, B).[88] Following these reports,

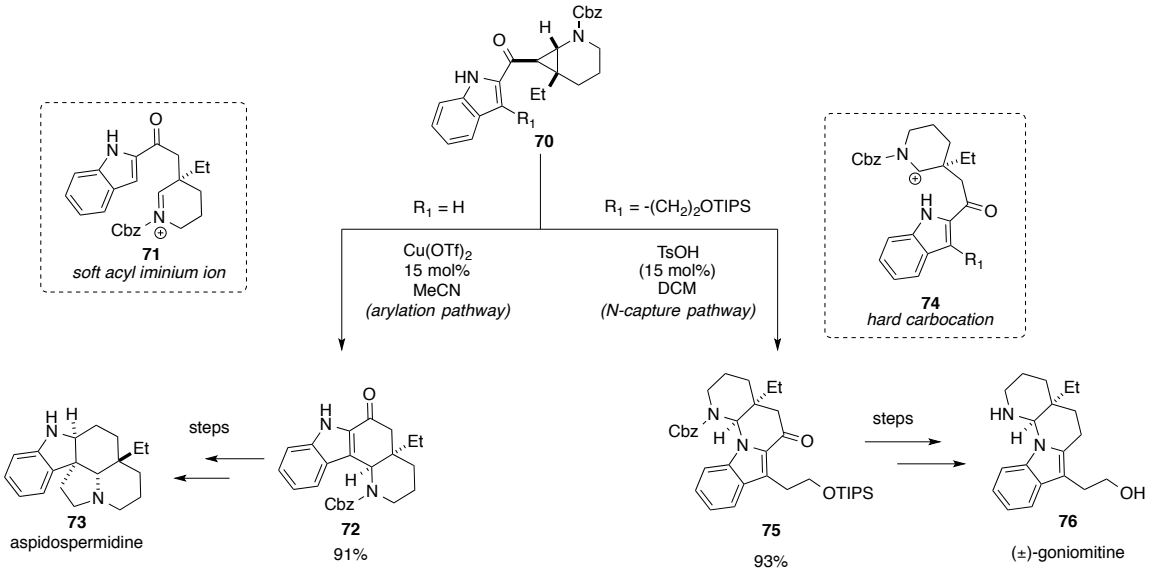
Marino et. al. utilized a similar approach for the formal synthesis of the bioactive natural product dihydrocompactin.[89] Other natural products, such as prostaglandins E and F, have analogously been synthesized.[90] Since these pioneering examples, many synthetic chemists have adopted D-A cyclopropanes for concise targeted syntheses of alkaloid, terpenoid, and steroid natural products.[66a]



Scheme 1.13. Ring-Opening Cyclizations of D-A Cyclopropanes and Application.

More recently, after almost 50 years since Stork's methodology, D-A cyclopropanes are still being employed in total synthesis. In an application by Waser et al., ring-opening cyclization transformations of D-A were found to be catalyst dependent (Scheme 1.14).[91] Using soft Lewis acid catalysts, such as $Cu(OTf)_2$, an arylative ring-opening cyclization smoothly afforded cyclohexa[*b*]indole **72**. Cbz deprotection of **72** concluded the formal synthesis of aspidospermidine (**73**),[92] an anticancer agent. On the other hand, catalytic amount of TsOH enable the formation of hydropyridoindole **75** via an *N*-capture pathway.[91] Hydropyridoindole **75** requires only a few steps to accomplish

the total synthesis of another anticancer compound; (±)-goniomitine (**76**). Presumably, the differential in cyclization pathways is due to whether acyl iminium intermediate **71** is formed in the transformation. The soft $Cu(OTf)_2$ Lewis acid was hypothesized to favor the formation of this intermediate which, in turn, led to cyclization via the softer indole C3 position. Conversely, a *hard-hard* interaction is experienced in the case of TsOH, where the *N*-atom quenches an intermediate carbocation on the piperidine ring in intermediate **74**.



Scheme 1.14. D-A Cyclopropanes for Divergent Synthesis of Indole Alkaloids.

1.4.7 Summary: cyclopropanes and their reactivity

For many decades, cyclopropanes have fascinated synthetic chemists due to their unique properties and unusual reactivity profiles. It has since been proven, beyond any reasonable doubt, that these strained carbocycles allow access to a variety of interesting scaffolds, either unachievable or difficult using any other precursors (Figure 1.5). As such, cyclopropanes allow rapid and concise entry into numerous carbocyclic and heterocyclic molecular scaffoldings. As a result of their immense value, many synthetic

chemists have dedicated considerable effort around cyclopropanes, both for their syntheses and their subsequent transformations into more complex, value-added intermediates or final products. Ultimately, the synthetic utility or cyclopropanes has been cemented through their use as building blocks for the total synthesis of natural products.

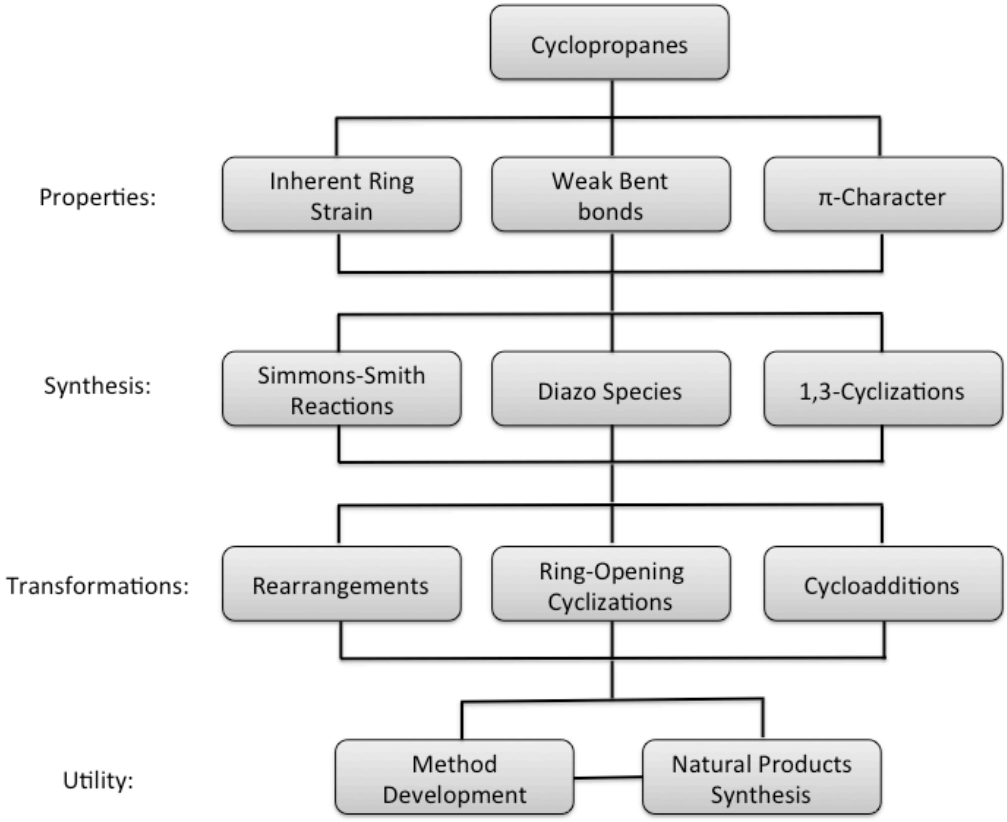


Figure 1.5. Overview of Importance of D-A Cyclopropanes in Chemical Synthesis.

1.5 Cyclobutane Building Blocks: Background and Bonding

Whereas cyclopropane has interested chemists for decades because of its unusual properties and reactivity as cycloalkane, cyclobutane represents the smallest cycloalkane with typical characteristics expected of regular, linear alkanes. As such, cyclobutane provides a kind of "bridge" between the odd properties of cyclopropane and the more

"normal" characteristic of larger-ring cycloalkanes. In an attempt to reduce significant torsional strain between its adjacent methylene groups, cyclobutane adopts a puckered conformation (two, inter-convertible forms) with a C-C-C bond angle of 88° (Figure 1.6).[93] While the puckered conformation leads to lowering of torsional strain, it also leads to a smaller C-C-C bond angle thus increasing angle strain. The balance between angle and torsional strain (total E_{strain} = 26.3 kcal/mol) dictates the equilibrium geometry. Another interesting aspect of the geometry of cyclobutane is that the methylene units are, surprisingly, rotated and point inwards in the puckered conformation.[94] This allows these CH_2-units to have local C_{2v} symmetry. Were it not for this symmetry, the planar conformation of cyclobutane might be expected to be more stable than the puckered one.

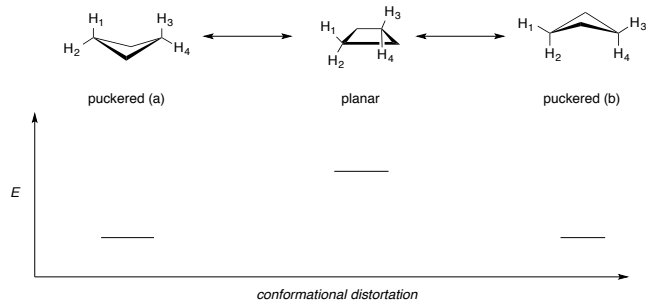


Figure 1.6. Conformations of Cycobutane.

One way of visualizing bonding in cyclobutane is by considering it as being constructed from CH_2-units, interacting with each other (Figure 1.6).[95] The sigma-type and p-type orbitals interact with themselves to produce bonding and anti-bonding orbitals. MO diagrams (Figure 1.7) represents the results of overlapping of those orbitals – orbitals on the left originate from sigma interactions while those on the right are from p interactions. The resulting MO picture has four, filled bonding orbitals accompanied by four, empty anti-bonding ones. As with cyclopropanes, cyclobutane C-C bonds have a

high degree of *p*-character, a property that leads to the C-H bonds being unusually strong due to their enhanced *s*-character.[96] The bond dissociation energy of C-H bonds in cyclobutane is 99.8 kcal/mol in comparison with 108.4 kcal/mol for cyclopropane.

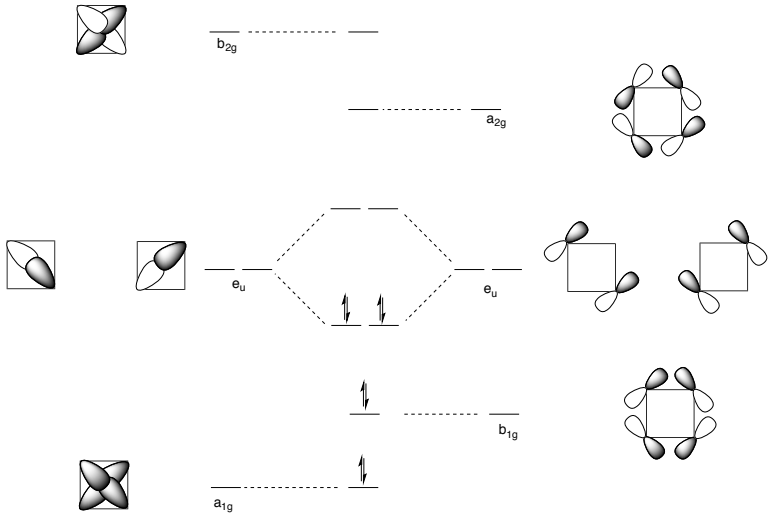


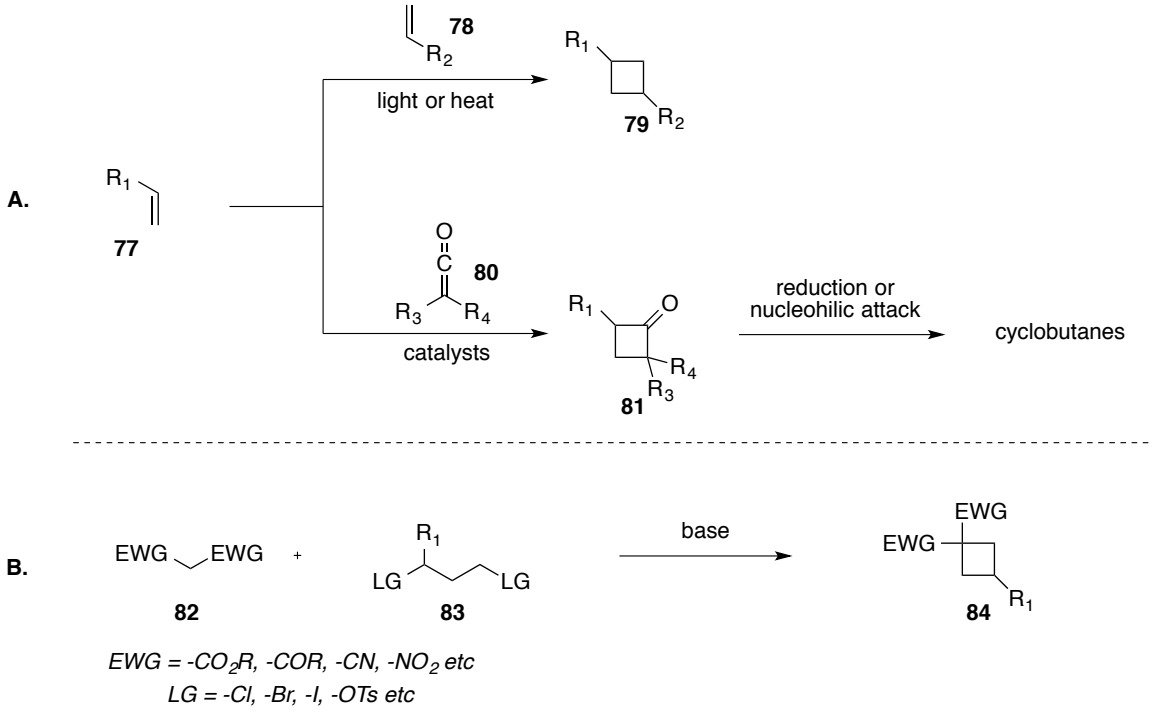
Figure 1.7. Molecular Orbital Diagram for Cyclobutane.

An interesting theory for bonding characteristics of cyclobutane involves σ-anti-aromaticity.[97] σ-Anti-aromaticity results due the eight electrons constrained in the cyclic C-C bonding framework. NMR evidence appears to be support this notion – cyclobutane has an abnormally low magnetic susceptibility and as well as ^{1}H and ^{13}C spectra that are deshielded. The paratropic ring current phenomenon would explain the observed NMR shifting in the cyclobutane and is an indicator of σ-aromaticity.

1.5.1 Synthesis of Cyclobutanes

Due to the ever-increasing utility of cyclobutanes in chemical transformations, many synthetic protocols have been developed for their synthesis. The most common precursors for cyclobutane synthesis are olefins, ketenes, and 1,3-dihaloalkanes. Using olefins and ketenes, [2+2]-cycloaddition reactions are employed to afford cyclobutanes or

cyclobutane precursors, respectively (Scheme 1.15, A).[98] On the other hand, with 1,3-dihaloalkanes or equivalents, double nucleophilic displacement reactions with a C^1 equivalent furnishes desired cyclobutane (Scheme 1.15, B).

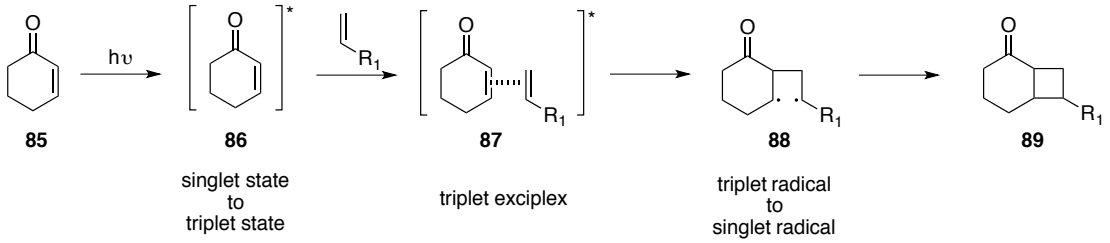


Scheme 1.15. Strategies for Cyclobutane Synthesis.

1.5.1.1 Photochemical [2+2] cycloadditions

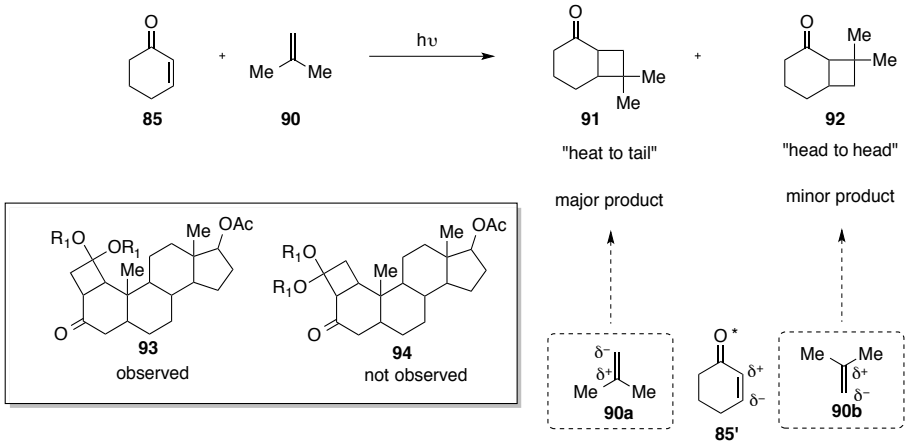
The photochemically-induced [2+2]-cycloaddition of two alkenes is allowed by the principles of orbital symmetry. Typically, this process involved excitation of electron from the HOMO (π in nature) to the LUMO (π^*) (Scheme 1.16).[96] The initial excited state is singlet in nature, and is relatively short-lived. Through intersystem crossing, the olefin decays into a triplet state.[99] The newly occupied orbital becomes a SOMO, and in this state, the activated alkene **86** can react with a neighboring alkene to form an exciplex **87**. Initial C-C bond formation then occurs leading to a triplet biradical **88** that, through a

spin inversion, proceeds to the singlet state. Finally, ring-closure occurs to afford the desired cyclobutane **89**.



Scheme 1.16. Mechanism for [2+2]-Photocycloaddition.

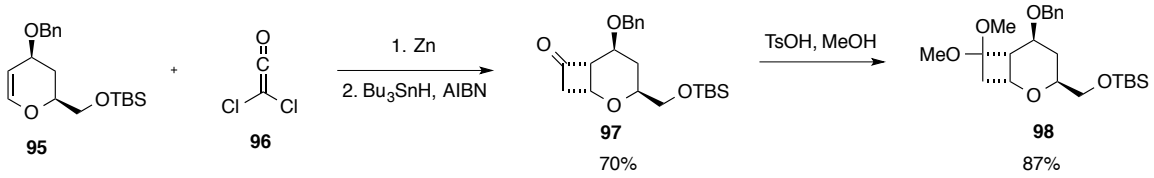
[2+2]-Photocycloadditions lead to very interesting stereochemical outcomes. In the excited state, an enone such as **85** typically has its polarity reversed as shown in intermediate **85'** (Scheme 1.17).[100] Given this consideration, isopropylene, in the configuration **90a**, offer the best match-up of dipoles leading to "head-to-tail" (HT) cyclobutane **91** as the predominant product. On the other hand, a less favored dipole interaction is depicted in configuration **90b** and affords cyclobutane **92** as the "head-to-head" (HH) minor product. This propensity for HH product formation is consistent across many other cyclohexenone precursors and can be enhanced by more polarized dipoles such as ketene acetals. This has been seen in the synthesis of cyclobutane-containing steroidal core **93**.[100a] Another interesting outcome of [2+2] photocycloadditions is the surprising formation of the less thermodynamically stable *trans*-cyclobutane HT products.[100a] In some cases, the *trans* product is actually formed in a higher ratio than the *cis* isomer.



Scheme 1.17. Stereochemical Outcomes for the [2+2]-Photocycloaddition.

1.5.1.2 [2+2] cycloadditions with ketenes

Ketenes are competent building blocks for cyclobutane synthesis.[101] In a representative example, 1,1-dicholoketene **96** undergoes Zn-mediated [2+2] cycloaddition and then dehalogenation to form cyclobutanone **97** (Scheme 1.18).[102] Ketenes typically react in a concerted fashion, forming cyclobutanones with retention of stereochemistry. Acetal-forming conditions using TsOH in MeOH then affords cyclobutane **98** in 87% yield.

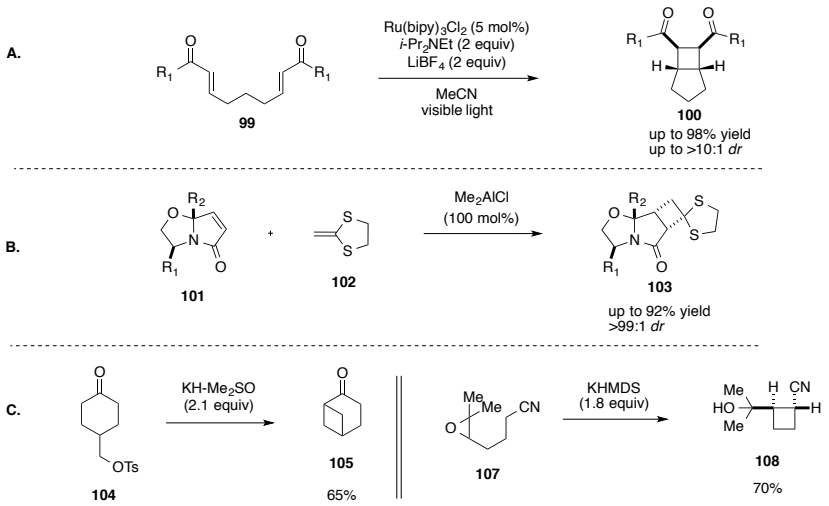


Scheme 1.18. Synthesis of Cyclobutanes Using Ketenes.

1.5.1.3 Other Cyclobutane-forming reactions

Many other strategies for synthesizing cyclobutanes have been developed.[103] For example, In the presence of visible light, Ru-based photocatalysis affords cyclopentane-fused cyclobutanes **100** in excellent yield and diastereoselectivity (Scheme 1.19, A)[104]

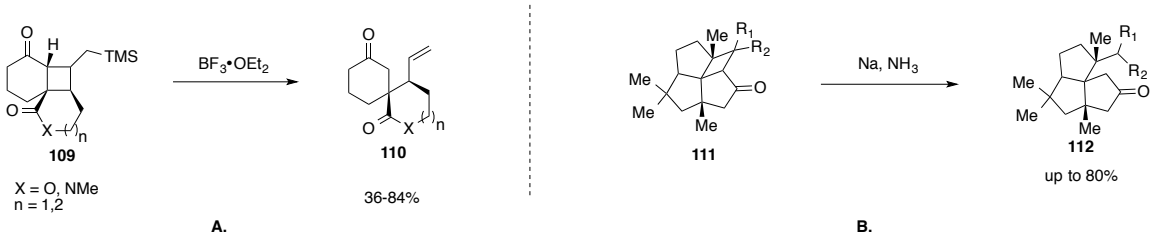
from dienones **99**. On the other hand, Al-mediated formal [2+2]-cycloadditions amide enes **101** and ketene acetal **102** produces cyclobutanes **103** as single diastereomers (Scheme 1.19, B).[105] Other methods include intramolecular 1,4-cyclizations under basic conditions to yield desired cyclobutanes **105** and **108** (Scheme 1.19, C).[106]



Scheme 1.19. Alternative Cyclobutane Syntheses.

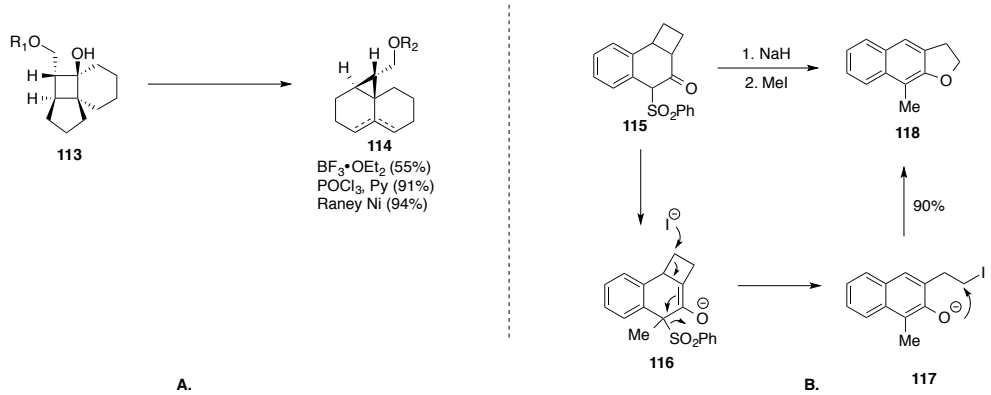
1.5.2 Cyclobutanes as Precursors in Method Development

Cyclobutanes have been utilized as precursors for a variety of important chemical scaffolds. Many of the transformations of cyclobutanes are driven by the consequential release of strain upon ring opening. BF_3•OEt_2-mediated ring-opening of cyclobutane **109**, for example, affords spirocyclic diketone **110** after desilylation (Scheme 1.20, A).[107] Various value-added spiro-products (lactones and lactams) are thus obtained in yields up to 84%. In another example, single-electron reduction of cyclobutane **111** using Na in NH_3 leads to tricyclopentanes **112** (Scheme 1.20, B).[108]



Scheme 1.20. Ring-Opening Reactions of Cyclobutanes.

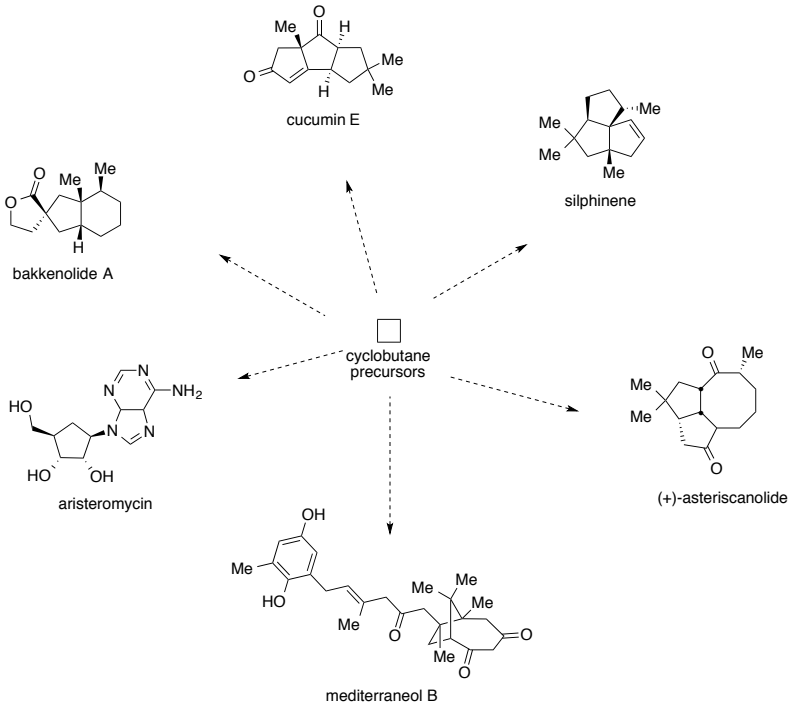
Other interesting ring-opening transformations include ring contractions and expansions. When subjected to BF_3•OEt_2, $POCl_3$, or Raney Ni, cyclobutane **113** was demonstrated to readily undergo ring-contractions to cyclopropanes **114** (Scheme 1.21, A)[109]. This transformation effectively converted a *5-4-6-* to *3-6-6* fused ring systems with yields ranging from 55% to 94%. In contrast, the enolate cyclobutane **115** undergoes nucleophilic attack and desulfurization to form intermediate **117** (Scheme 1.21, B)[110]. Formation of intermediate **117** is also driven by an eventual thermodynamic sink - aromatization. Finally, an intramolecular nucleophilic displacement furnishes naphthalene-fused tetrahydrofuran **118**.



Scheme 1.21. Ring Contractions and Expansions of Cyclobutanes.

1.5.3 Cyclobutanes as Building Blocks in Total Synthesis

As testament to their synthetic utility, cyclobutanes have found use as precursors to a variety of natural products (Scheme 1.22).[111] Their versatility enables rapid complexity generation of polycyclic scaffolds. Using strategic cyclobutanations and ring-opening approaches, synthetic transformations that would otherwise be laborious can be undertaken in a more step-economic fashion. Through judicious use of substituents and reaction conditions, chemical transformations can be effected in a stereoselective manner and under mild reaction conditions. As such, cyclobutanes have been recognized as invaluable building blocks to synthetic chemists.

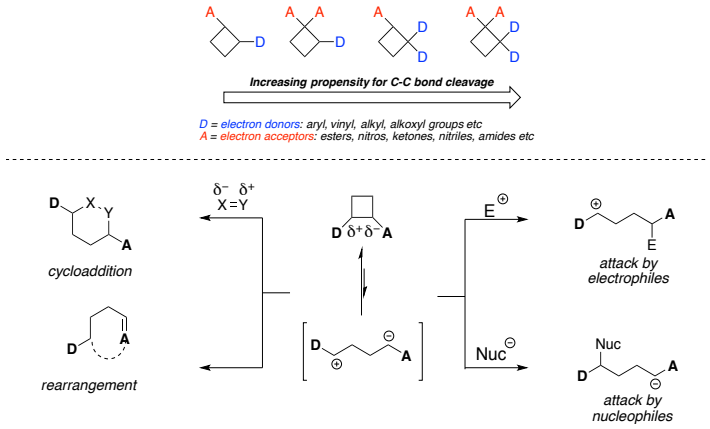


Scheme 1.22. Acessible Natural Products Using Cyclobutane Precursors.

1.6 A Special Class of Cyclobutanes: The D-A Cyclobutanes

Among cyclobutanes is a special class of the building blocks for chemical synthesis - the donor-acceptor (D-A) cyclobutanes.[112] Coupled with ring strain (approx.

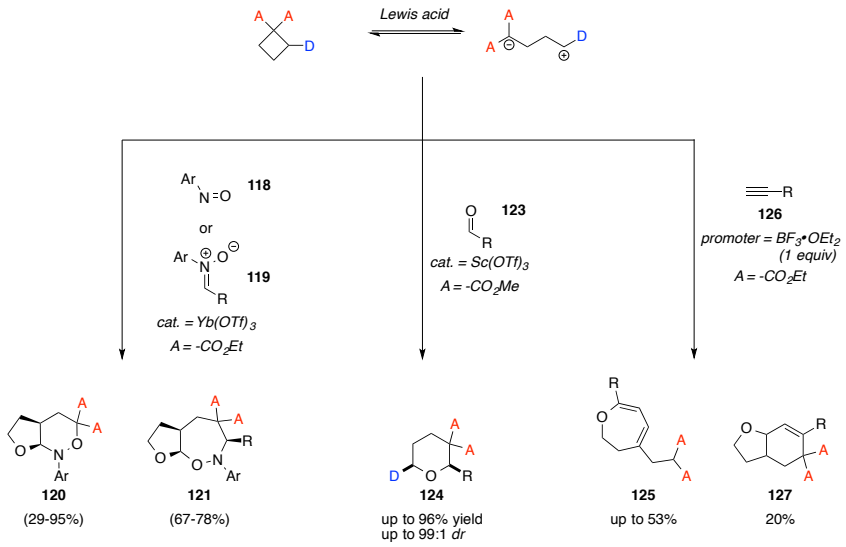
26 kcal/mol), vicinal substitution with electron donating and electron withdrawing groups on cyclobutanes allow for increased propensity towards ring opening (Scheme 1.23). As an added advantage, the adjoining bond, C(1)-C(2), is the weakest allowing for predictability of C-C bond fission upon Lewis acid activation. This reactivity is similar to the analogous and well-studied D-A cyclopropanes.[67d, 70, 113] Ring-opening transformations of cyclobutanes typically affords 1,4-zwitterionic synthons, intermediates capable of undergoing divergent reactivity including: (1) cycloadditions; (2) rearrangements; and (3) attack by electrophiles and nucleophiles.[112]



Scheme 1.23. Reactivity of D-A Cyclobutanes.

It is conceivable that since D-A cyclobutanes and cyclopropanes bear strong similarities (in ring strain and barrier to ring-opening), they should undergo reasonably similar reactivity. Guided by the extensively studied D-A cyclopropane reactivity, many synthetic chemists have made significant strides to invent analogous reactions for D-A cyclobutanes. As a result, one such area of reactivity that has gained much traction recently is the [4+*n*]-cycloaddition reactions.[114] Examples of this transformation include reactions of D-A cyclobutanes with arylnitroso compounds **118** and nitrones **119** to afford tetrahydrooxazines **120** (formal [4+2] cycloaddition)[115] and oxazepines **121**

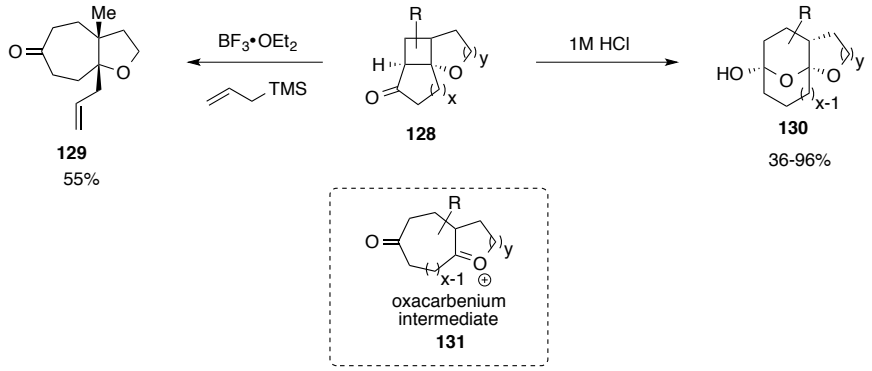
(formal [4+3] cycloadditions),[116] respectively (Scheme 1.24). These reactions, catalyzed by $Yb(OTf)_3$, involve nitroso compounds and nitrones acting as dipolarophiles allowing smooth reactivity in good to high yields. Other dipolarophiles, such aldehydes **123**, are also possible. Upon reacting the D-A cyclobutanes in the presence of catalytic $Sc(OTf)_3$, functionalized tetrahydropyrans **124** can be synthesized in high yields and excellent diastereoselectivity.[117] In other examples, utilization of alkyne dipolarophiles **126** furnishes dihdrooxepines **125** and fused tetrahydrofurans **127** in a chemodivergent fashion.[118]



Scheme 1.24. Formal Cycloaddition Reactions Using D-A Cyclobutanes.

The examples indicated (Scheme 1.24) demonstrated the potential of D-A cyclobutanes to undergo transformations analogous to their cyclopropane counterparts. D-A cyclopropanes have historically received much more attention than D-A cyclobutanes and therefore are more extensively studied.[67d] However, a recent trend shows increasing popularity of D-A cyclobutanes as subjects for methodology development. Evidence of this progress is indicated by the development of interesting

reactions using D-A cyclobutane **128** (Scheme 1.25).[119] Presumably, in the presence of 1M HCl, cyclobutane **128** undergoes a ring-opening whereby the intermediate oxacarbenium ion **131** is trapped by H_2O to form an intermediate hemiacetal. This hemiacetal can then undergo an intramolecular nucleophilic attack onto the ketone afford densely fused acetals **130** as the final products. On the other hand, the oxacarbenium ion **131** can also undergo a Hosomi-Sakurai-type allylation using ally-TMS to form bicyclic compound **129**.



Scheme 1.25. Other Ring-Opening Reactions of D-A Cyclobutanes.

1.6.1 Summary: Cyclobutanes and Their Reactivity

Cyclobutanes are unique since they bridge the gap between the highly unusual cyclopropane with the larger cycloalkanes. Armed with an equivalent degree of ring strain, cyclobutanes can undergo rearrangement and ring-opening reactivity analogous to cyclopropanes (Figure 1.8). As result, cyclobutanes allow entry into chemical scaffolds complementary to those of corresponding cyclopropanes. In investigating cyclobutanes, synthetic chemists have begun to appreciate that cyclobutanes are formidable synthetic precursors in their own right, offering compelling transformations into unique molecular targets. Given this insight, the number of reports utilizing cyclobutanes is on the rise. It is

therefore not inconceivable that cyclobutanes may one day blossom into prominent "go-to" building blocks for chemical synthesis.

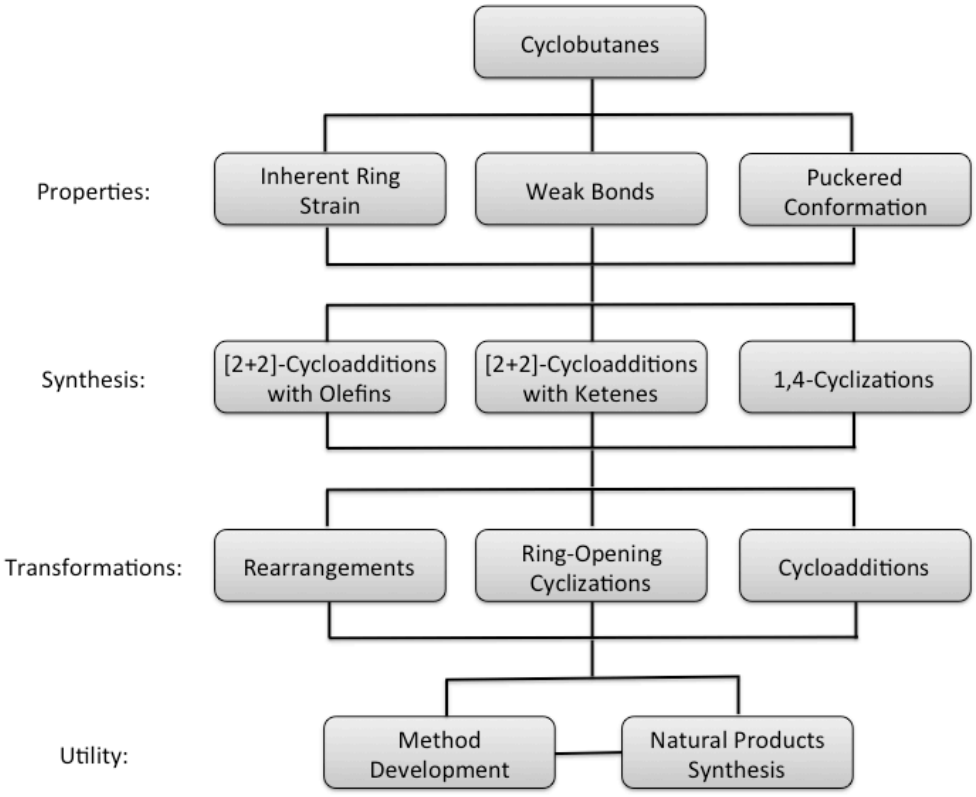


Figure 1.8. The Chemistry of Cyclobutanes.

1.7 Scope of Thesis

This thesis demonstrates novel uses of strained carbocycles (D-A cyclopropanes and D-A cyclobutanes) in both methodology development and application (Figure 1.9). At the beginning of each chapter, an exhaustive review of prior approaches to transformation of interest is carried out. The goals of such reviews are primarily three-fold: (1) to discuss to the chosen synthetic phenomena in the proper historical context; (2) to fairly assess these prior synthetic approaches and ascertain their strengths and weaknesses (in terms of choice and loading of Lewis acids, harshness of reactions

conditions, breadth of substrate scope, efficiency, and versatility); and (3) to justify our performed synthetic endeavors as being important additions to the field of interest and to the synthetic community in general.

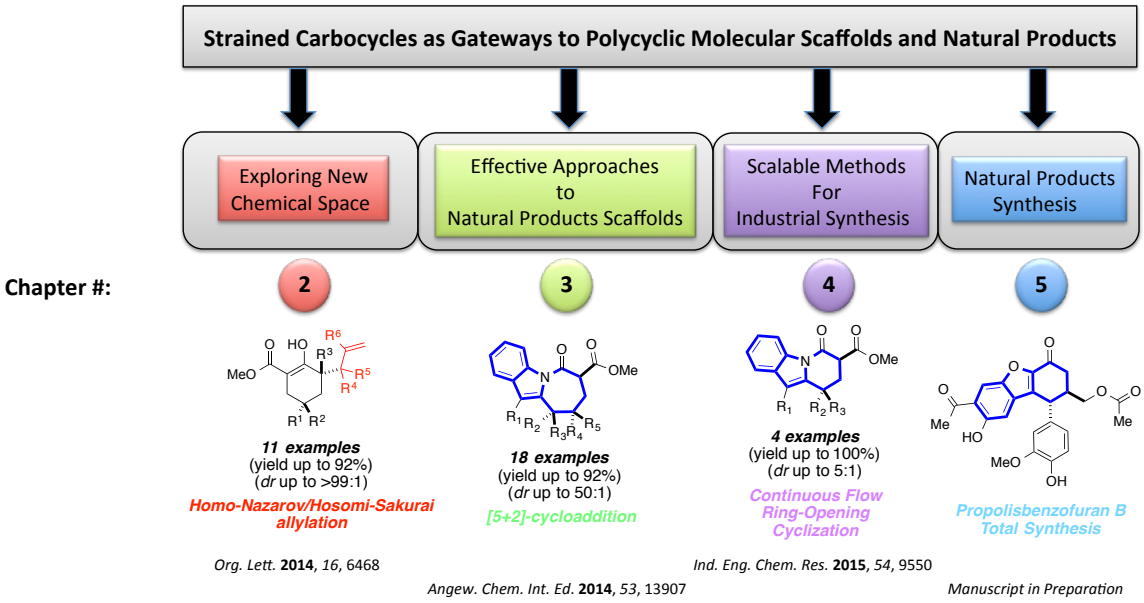


Figure 1.9. Scope of Dissertation.

Chapter Two, the "Exploratory Chemistry" chapter, recognizes the young and budding field of homo-Nazarov chemistry as being rich in potential areas of exploration (Figure 1.9). Discussed in this chapter is the history of the homo-Nazarov reaction all the way from its conception (which was inspired by the parent Nazarov cyclization) to the present day catalytic and efficient variations. Over the past decade, one of the biggest challenges for this reaction has been to lower the amounts of Lewis or Bronsted acids to sub-stoichiometric or catalytic levels. The France lab, together with other groups, has been able to address this issue. More importantly, we have been able to develop chemodivergent, interrupted homo-Nazarov variations under mild catalytic conditions.

These interrupted variations offer new methods that we hope will propel the synthetic community into recognizing the utility of the homo-Nazarov cyclization and its variants. A tale of the genesis, rationale and effectuation of the catalytic interrupted homo-Nazarov reaction is expounded upon in detail. Of note is the use of an ester group as the secondary acceptor on the D-A-A cyclopropane, which leads, directly, to catalysis and regioselectivity. Interruption reactions are carried out using allylsilane, arene, and heteroarene nucleophiles to form a broad range of highly functionalized cyclohexanones and cyclohexenols. "Exploration as a trigger for synthetic novelty and utility", is the catch phrase for Chapter Two.

Moving away from the exploratory nature of Chapter Two, Chapter Three shifts emphasis entirely. This chapter recognizes and elaborates the importance of azepino[1,2-*a*]indoles as scaffolds in numerous indole alkaloid natural products (Figure 1.9). A survey of literature methods for synthesis of this scaffolding is performed and reveals a deficiency: the lack of efficient and generalized protocols for synthesis of azepino[1,2-*a*]indoles. This deficiency is immediately recognized as an opportunity. Given our continued interest in strained carbocycles, this chapter invokes D-A cyclobutanes as precursors to azepino[1,2-*a*]indoles. Furthermore, a method is developed in which the D-A cyclobutanes need not be synthesized and isolated separately for a subsequent cycloisomerizations. Indeed, D-A cyclobutanes are thus synthesized in situ via formal [5+2] cycloadditions of alkenes and alkylidenes for furnish desired azepino[1,2-*a*]indoles in high yields, diastereoselectivities and under mild Lewis acid catalytic conditions. This azepino[1,2-*a*]indole synthesis is then used to as inspiration for the synthesis of cyclohepta[*b*]indoles, another important chemical scaffold in the indole alkaloid family

of natural products. “Recognition of the underutilization of D-A cyclobutanes as versatile synthetic building blocks” best describes the motivation and summary of Chapter Three.

In Chapter Four, the gear is shifted again. This chapter develops a methodology with mostly one specific target audience in mind - industry. This chapter discusses a previous methodology first conceived in the France lab; the ring-opening cyclization of D-A cyclopropanes to afford important hydropyrido[1,2-*a*]indole scaffolds (Figure 1.9). Addressed in this chapter is a tale of the development of an unprecedented tandem, bicatalytic cyclopropanation-ring-opening cyclization protocol for the high throughput synthesis of hydropyrido[1,2-*a*]indoles using continuous flow technology. The sheer complexity of this idea upon its conception is recognized, and this led to partnering with some wonderful chemical engineers from the Eckert-Liotta lab. Through this collaboration, transfer of the tandem protocol from batch to a continuous flow setup was successfully effectuated.

Chapter Five attempts to maintain a theme conceived in Chapter Four: the development, and more importantly, application of a methodology towards a specific goal. In the case of Chapter Five, the goal is the development of a stepwise intramolecular cyclopropanation then intramolecular ring-opening cyclization to afford unprecedented lactone-fused heteroaromatics (Figure 1.9). Furthermore, it is highlighted that this protocol could prove very valuable for a concise synthesis of propolisbenzofuran B, a bioactive natural product. A reasonable retrosynthesis, as well as forward synthesis of a model system, is demonstrated as evidence towards the utility of this synthetic protocol. “Cycloisomerization with a twist: densely functionalized D-A cyclopropanes *en route* to propolisbenzofuran B” neatly sums up efforts performed in this chapter.

Finally, Chapter Six attempts to summarize findings of all preceding chapters, the value of D-A cyclopropane and cyclobutanes, and will proffer potential future possibilities as a result of data from this thesis.

1.8 REFERENCES

1. (a) Wen, J.; Wilkes, G. L., Organic/Inorganic Hybrid Network Materials by the Sol−Gel Approach. *Chem. Mater.* **1996,** *8* (8), 1667-1681; (b) Lutz, J. F.; Nanotechnology for Life Science Research, G., 1,3-dipolar cycloadditions of azides and alkynes: a universal ligation tool in polymer and materials science. *Angew. Chem. Int. Ed. Engl.* **2007,** *46* (7), 1018-25; (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S., Recent advances in the transition metal-catalyzed twofold oxidative C-H bond activation strategy for C-C and C-N bond formation. *Chem. Soc. Rev.* **2011,** *40* (10), 5068-83; (d) Liu, L.-H., Perfluorophenyl azides: new applications in surface functionalization and nanomaterial synthesis. *Acc. Chem. Res.* **2010,** *43* (11), 1434-1443; (e) Nandivada, H., Click chemistry: versatility and control in the hands of materials scientists. *Adv. Mater.* **2010,** *19* (17), 2197-2208.

2. (a) Chernyshkova, F., Heteropoly acids and their salts - novel promising catalysts for petrochemical and organic synthesis. *Neftekhimiya* **1991,** *31* (5), 579-591; (b) Isakov Ya, I., Use of zeolite catalysts in petrochemistry and organic synthesis. *Neftekhimiya* **1998,** *38* (6), 404-438; (c) Karakhanov, E., Design of supramolecular metal complex catalytic systems for organic and petrochemical synthesis. *Russ. Chem. Rev.* **2005,** *74* (1), 97-111.

3. (a) Aleu, J., Biocatalysis applied to the synthesis of agrochemicals. *Curr. Org. Chem.* **2006,** *10* (16), 2037-2054; (b) Fischer, H. P., Synthesis and chirality of novel heterocyclic compounds designed for crop protection. *Bull. Soc. Chim. Belg.* **1994,** *103* (9-10), 565-581; (c) Grondal, C., Organocatalytic cascade reactions as a new tool in total

synthesis. *Nat. Chem.* **2010,** *2* (3), 167-178; (d) Copping, L. G.; Duke, S. O., Natural products that have been used commercially as crop protection agents. *Pest Manag. Sci.* **2007,** *63* (6), 524-554.

4. (a) Magano, J., Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **2011,** *111* (3), 2177-2250; (b) Botteghi, C.; Paganelli, S.; Schionato, A.; Marchetti, M., The asymmetric hydroformylation in the synthesis of pharmaceuticals. *Chirality* **1991,** *3* (4), 355-369; (c) Dömling, A.; Ugi, I., Multicomponent Reactions with Isocyanides. *Angew. Chem. Int. Ed.* **2000,** *39* (18), 3168-3210; (d) Schreiber, S. L., Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **2000,** *287* (5460), 1964-1969.

5. Alonso, H.; Bliznyuk, A. A.; Gready, J. E., Combining docking and molecular dynamic simulations in drug design. *Med. Res. Rev.* **2006,** *26* (5), 531-568.

6. Oprea, T. I.; Davis, A. M.; Teague, S. J.; Leeson, P. D., Is There a Difference between Leads and Drugs? A Historical Perspective. *J. Chem. Inf. Comput. Sci.* **2001,** *41* (5), 1308-1315.

7. (a) Wender Paul, A., Miller, B. L.; Toward the ideal synthesis: connectivity analysis and multibond-forming processes. *Organic Synthesis: Theory and Applications* **1993,** *2*, 27-66; (b) Trost, B. M., Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed.* **1995,** *34* (3), 259-281; (c) Wender, P. A., Introduction: Frontiers in Organic Synthesis. *Chem. Rev.* **1996,** *96* (1), 1-2; (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G., Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry. *Angew. Chem. Int. Ed.* **2008,** *47* (33), 6138-6171; (e) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.;

Genazzani, A. A., Click chemistry reactions in medicinal chemistry: Applications of the 1,3-dipolar cycloaddition between azides and alkynes. *Med. Res. Rev.* **2008,** *28* (2), 278-308; (f) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H., Function-Oriented Synthesis, Step Economy, and Drug Design. *Acc. Chem. Res.* **2008,** *41* (1), 40-49; (g) Young, I. S.; Baran, P. S., Protecting-group-free synthesis as an opportunity for invention. *Nat. Chem.* **2009,** *1* (3), 193-205; (h) Gaich, T.; Baran, P. S., Aiming for the Ideal Synthesis. *J. Org. Chem.* **2010,** *75* (14), 4657-4673; (i) Wender, P. A., Toward the ideal synthesis and molecular function through synthesis-informed design. *Nat. Prod. Rep.* **2014,** *31* (4), 433-440; (j) Andrushko, V.; Andrushko, N., Principles, Concepts and Strategies of Stereoselective Synthesis. In *Stereoselective Synthesis of Drugs and Natural Products*, John Wiley & Sons, Inc.: **2013**.

8. Kingston, D. G. I., Taxol, a molecule for all seasons. *Chem. Commun.* **2001,** (10), 867-880.

9. Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M., Total Synthesis of Ciguatoxin CTX3C. *Science* **2001,** *294* (5548), 1904-1907.

10. (a) Godula, K.; Sames, D., C-H Bond Functionalization in Complex Organic Synthesis. *Science* **2006,** *312* (5770), 67-72; (b) Ménard, G.; Stephan, D. W., Room Temperature Reduction of CO2 to Methanol by Al-Based Frustrated Lewis Pairs and Ammonia Borane. *J. Am. Chem. Soc.* **2010,** *132* (6), 1796-1797; (c) Jiang, C.; Blacque, O.; Fox, T.; Berke, H., Reversible, metal-free hydrogen activation by frustrated Lewis pairs. *Dalton Trans.* **2011,** *40* (5), 1091-1097.

11. (a) Overman, L. E.; Pennington, L. D., Strategic Use of Pinacol-Terminated Prins Cyclizations in Target-Oriented Total Synthesis. *J. Org. Chem.* **2003,** *68* (19), 7143-

7157; (b) Weinreb, S. M., Lepadiformine: A Case Study of the Value of Total Synthesis in Natural Product Structure Elucidation. *Acc. Chem. Res.* **2003,** *36* (1), 59-65.

12. Nicolaou, K.; Nicolaou, K. C., *Classics in Total Synthesis*. VCH: Weinheim, Germany, **1996**.

13. Danishefsky, S. J., Complex Target-Oriented Synthesis in the Drug Discovery Process: A Case History in the dEpoB Series. *J. Org. Chem.* **1999,** *64* (23), 8434-8456.

14. Wilson, R. M.; Danishefsky, S. J., Pattern Recognition in Retrosynthetic Analysis: Snapshots in Total Synthesis. *J. Org. Chem.* **2007,** *72* (12), 4293-4305.

15. Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B., Organocatalytic One-Pot Asymmetric Synthesis of Functionalized Tricyclic Carbon Frameworks from a Triple-Cascade/Diels–Alder Sequence. *Angew. Chem. Int. Ed.* **2007,** *46* (3), 467-469.

16. (a) Towle, M. J.; Salvato, K. A.; Budrow, J.; Wels, B. F.; Kuznetsov, G.; Aalfs, K. K.; Welsh, S.; Zheng, W.; Seletsky, B. M.; Palme, M. H., In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res.* **2001,** *61* (3), 1013-1021; (b) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J., The Total Synthesis of Dynemicin A Leading to Development of a Fully Contained Bioreductively Activated Enediyne Prodrug. *J. Am. Chem. Soc.* **1996,** *118* (40), 9509-9525.

17. Dandapani, S.; Marcaurelle, L. A., Current strategies for diversity-oriented synthesis. *Curr. Opin. Chem. Biol.* **2010,** *14* (3), 362-370.

18. (a) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J., Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. *Science* **1999,** *286* (5441), 971-974; (b) Spaller, M. R.; Burger,

M. T.; Fardis, M.; Bartlett, P. A., Synthetic strategies in combinatorial chemistry. *Curr. Opin. Chem. Biol.* **1997,** *1* (1), 47-53.

19. Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R., Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. *Nat. Commun.* **2010,** *1*, 80.

20. Paulvannan, K., Preparation of tricyclic nitrogen heterocycles via tandem four-component condensation/intramolecular Diels-Alder reaction. *Tetrahedron Lett.* **1999,** *40* (10), 1851-1854.

21. Newman, D. J.; Cragg, G. M.; Snader, K. M., The influence of natural products upon drug discovery (Antiquity to late 1999). *Nat. Prod. Rep.* **2000,** *17* (3), 215-234.

22. (a) Lee, K.-H., Current Developments in the Discovery and Design of New Drug Candidates from Plant Natural Product Leads. *J. Nat. Prod.* **2004,** *67* (2), 273-283; (b) Galliford, C. V.; Scheidt, K. A., Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem. Int. Ed. Engl.* **2007,** *46* (46), 8748-58; (c) Mishra, B. B.; Tiwari, V. K., Natural products: an evolving role in future drug discovery. *Eur. J. Med. Chem.* **2011,** *46* (10), 4769-807; (d) Williams, P.; Sorribas, A.; Howes, M. J., Natural products as a source of Alzheimer's drug leads. *Nat. Prod. Rep.* **2011,** *28* (1), 48-77; (e) Bolzani, V. d. S.; Valli, M.; Pivatto, M.; Viegas, C., Natural products from Brazilian biodiversity as a source of new models for medicinal chemistry. *Pure Appl. Chem.* **2012,** *84* (9).

23. (a) Wink, M., Plant breeding: importance of plant secondary metabolites for protection against pathogens and herbivores. *Theoret. Appl. Genetics* **1988,** *75* (2), 225-233; (b) Goossens, A.; Hakkinen, S. T.; Laakso, I.; Seppanen-Laakso, T.; Biondi, S.; De

Sutter, V.; Lammertyn, F.; Nuutila, A. M.; Soderlund, H.; Zabeau, M.; Inze, D.; Oksman-Caldentey, K. M., A functional genomics approach toward the understanding of secondary metabolism in plant cells. *Proc. Natl. Acad. Sci. USA.* **2003,** *100* (14), 8595-600.

24. Luo, Y.; Cobb, R. E.; Zhao, H., Recent advances in natural product discovery. *Curr. Opin. Biotechnol.* **2014,** *30*, 230-7.

25. Zerikly, M.; Challis, G. L., Strategies for the Discovery of New Natural Products by Genome Mining. *ChemBioChem* **2009,** *10* (4), 625-633.

26. Lautru, S.; Deeth, R. J.; Bailey, L. M.; Challis, G. L., Discovery of a new peptide natural product by Streptomyces coelicolor genome mining. *Nat. Chem. Biol.* **2005,** *1* (5), 265-269.

27. Li, J. W. H.; Vederas, J. C., Drug Discovery and Natural Products: End of an Era or an Endless Frontier? *Science* **2009,** *325* (5937), 161-165.

28. Drews, J., Drug Discovery: A Historical Perspective. *Science* **2000,** *287* (5460), 1960-1964.

29. (a) Harborne, J. B., *Phytochemical Dictionary: A Handbook of Bioactive Compounds from Plants, Second Edition*. TaylorFrancis: London, UK, **1999**; (b) The classes of natural product and their isolation. In *Natural Products: The Secondary Metabolites*, Hanson, J. R., Ed. The Royal Society of Chemistry: **2003**; Vol. 17, pp 1-34; (c) Boonnak, N.; Karalai, C.; Chantrapromma, S.; Ponglimanont, C.; Kanjana-Opas, A.; Chantrapromma, K.; Fun, H.-K., Quinonoids from the barks of Cratoxylum formosum subsp.pruniflorum. *Can. J. Chem.* **2007,** *85* (5), 341-345.

30. (a) Hassner, A.; Murthy, K. S. K.; Maurya, R.; Dehaen, W.; Friedman, O., Stereoselectivity during cycloadditions leading to functionalized heterocycles. *J. Heterocycl. Chem.* **1994,** *31* (3), 687-694; (b) Poulin, J.; Grise-Bard, C. M.; Barriault, L., Pericyclic domino reactions: concise approaches to natural carbocyclic frameworks. *Chem. Soc. Rev.* **2009,** *38* (11), 3092-3101; (c) Alonso, R.; Caballero, A.; Campos, P. J.; Rodríguez, M. A., Photochemistry of acyloximes: synthesis of heterocycles and natural products. *Tetrahedron* **2010,** *66* (46), 8828-8831; (d) Fujiwara, Y.; Dixon, J. A.; O/'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S., Practical and innate carbon-hydrogen functionalization of heterocycles. *Nature* **2012,** *492* (7427), 95-99.

31. (a) Blumenkopf, T. A.; Overman, L. E., Vinylsilane-and alkynylsilane-terminated cyclization reactions. *Chem. Rev.* **1986,** *86* (5), 857-873; (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A., Palladium-catalyzed inter-and intramolecular cross-coupling reactions of B-alkyl-9-borabicyclo [3.3. 1] nonane derivatives with 1-halo-1-alkenes or haloarenes. Syntheses of functionalized alkenes, arenes, and cycloalkenes via a hydroboration-coupling sequence. *J. Am. Chem. Soc.* **1989,** *111* (1), 314-321; (c) Fairlamb, I. J. S., Asymmetric Cycloisomerization of 1, 6‐and 1, 7‐Enynes by Transition‐Metal Catalysts. *Angew. Chem. Int. Ed.* **2004,** *43* (9), 1048-1052; (d) Itoh, T.; Mase, T., A novel practical synthesis of benzothiazoles via Pd-catalyzed thiol cross-coupling. *Org. Lett.* **2007,** *9* (18), 3687-3689; (e) Shen, H. C., Recent advances in syntheses of heterocycles and carbocycles via homogeneous gold catalysis. Part 1: Heteroatom addition and hydroarylation reactions of alkynes, allenes, and alkenes. *Tetrahedron* **2008,** *64* (18), 3885-3903; (f) Krause, N.; Winter, C., Gold-

catalyzed nucleophilic cyclization of functionalized allenes: a powerful access to carbo- and heterocycles. *Chem. Rev.* **2011,** *111* (3), 1994-2009; (g) Müller, T. J., Synthesis of Carbo-and Heterocyclesvia Coupling-Isomerization Reactions. *Synthesis* **2012,** *2012* (02), 159-174; (h) Yet, L., Metal-mediated synthesis of medium-sized rings. *Chem. Rev.* **2000,** *100* (8), 2963-3008.

32. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C., Ring-closing metathesis and related processes in organic synthesis. *Acc. Chem. Res.* **1995,** *28* (11), 446-452; (b) Michaut, A.; Rodriguez, J., Selective Construction of Carbocyclic Eight‐Membered Rings by Ring‐Closing Metathesis of Acyclic Precursors. *Angew. Chem. Int. Ed.* **2006,** *45* (35), 5740-5750; (c) Maier, M. E., Synthesis of Medium‐Sized Rings by the Ring‐Closing Metathesis Reaction. *Angew. Chem. Int. Ed.* **2000,** *39* (12), 2073-2077.

33. (a) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L., The Cycloaddition Strategy for the Synthesis of Natural Products Containing Carbocyclic Seven‐Membered Rings. *Chem. Eur. J.* **2006,** *12* (13), 3438-3447; (b) Poulin, J.; Grisé-Bard, C. M.; Barriault, L., Pericyclic domino reactions: concise approaches to natural carbocyclic frameworks. *Chem. Soc. Rev.* **2009,** *38* (11), 3092-3101; (c) Ylijoki, K. E. O.; Stryker, J. M., [5+ 2] Cycloaddition Reactions in Organic and Natural Product Synthesis. *Chem. Rev.* **2012,** *113* (3), 2244-2266; (d) Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D., Catalysis of 6π electrocyclizations. *Angew. Chem. Int. Ed.* **2008,** *47* (42), 8100-8103.

34. (a) Ishibashi, H.; Sato, T.; Ikeda, M., 5-Endo-trig radical cyclizations. *Synthesis* **2002,** (6), 695-713; (b) Yet, L., Free radicals in the synthesis of medium-sized rings. *Tetrahedron* **1999,** *55* (31), 9349-9403.

35. (a) Ihara, M., Syntheses of Biologically Active Natural Products and Leading Compounds for New Pharmaceuticals Employing Effective Construction of a Polycyclic Skeleton. *Chem. Pharm. Bull.* **2006,** *54* (6), 765-774; (b) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J., Development of Cascade Reactions for the Concise Construction of Diverse Heterocyclic Architectures. *Acc. Chem. Res.* **2012,** *45* (8), 1278-1293.

36. (a) Aggarwal, V. K., Organic synthesis: New uses for old building blocks. *Nat Chem* **2009,** *1* (6), 433-434; (b) Corey, E. J.; Kurti, L., *Enantioselective Chemical Synthesis: Methods, Logic, and Practice*. Elsevier: **2013**; (c) Wade, L. G., Organic Synthesis: The Disconnection Approach (Warren, Stuart). *J. Chem. Educ.* **1984,** *61* (9), A248.

37. (a) Zimmer, R., Alkoxyallenes: building blocks in organic synthesis. *Synthesis* **1993,** (2), 165-178; (b) Ma, S., Some typical advances in the synthetic applications of allenes. *Chem. Rev.* **2005,** *105* (7), 2829-2872.

38. Trost, B. M., On Inventing Reactions for Atom Economy. *Acc. Chem. Res.* **2002,** *35* (9), 695-705.

39. Pandey, G.; Banerjee, P.; Gadre, S. R., Construction of enantiopure pyrrolidine ring system via asymmetric [3+ 2]-cycloaddition of azomethine ylides. *Chem. Rev.* **2006,** *106* (11), 4484-4517.

40. Zhang, Z.; Wang, J., Recent studies on the reactions of α-diazocarbonyl compounds. *Tetrahedron* **2008,** *64* (28), 6577-6605.

41. Watson, I. D. G.; Yu, L.; Yudin, A. K., Advances in Nitrogen Transfer Reactions Involving Aziridines. *Acc. Chem. Res.* **2006,** *39* (3), 194-206.

42. Smith, J., Synthetically useful reactions of epoxides. *Synthesis* **1984,** (8), 629-656.

43. Hedley, S. J.; Ventura, D. L.; Dominiak, P. M.; Nygren, C. L.; Davies, H. M. L., Investigation into Factors Influencing Stereoselectivity in the Reactions of Heterocycles with Donor−Acceptor-Substituted Rhodium Carbenoids. *J. Org. Chem.* **2006,** *71* (14), 5349-5356.

44. (a) Sugden, T., Structure of cyclopropane and ethylene oxide. *Nature* **1947,** *160*, 367-368; (b) Walsh, A., Structures of ethylene oxide, cyclopropane, and related molecules. *Trans. Faraday Soc.* **1949,** *45*, 179-190.

45. (a) Walsh, A., Structures of ethylene oxide and cyclopropane. *Nature 159*, 712-713; (b) Walsh, A. D., The structures of ethylene oxide, cyclopropane, and related molecules. *Trans. Faraday Soc.* **1949,** *45* (0), 179-190.

46. (a) Coulson, C., Strain in nontetrahedral carbon atoms. *J. Chem. Phys.* **1947,** *15*, 151-0; (b) Coulson, C., The properties of certain strained hydrocarbons. *Philos. Mag. (1798-1977)* **1949,** *40*, 1-35; (c) Forster, T., The mutual influence of valences in the carbon atom. *Z. physik. Chem.* **1939,** *B43*, 58-78.

47. (a) Luo, Y.-R.; Luo, Y.-R., *Handbook of Bond Dissociation Energies in Organic Compounds*. CRC Press: Boca Raton, Fla, **2002**; (b) Blanksby, S. J.; Ellison, G. B., Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003,** *36* (4), 255-263.

48. Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T., Use of cyclopropanes and their derivatives in organic synthesis. *Chem. Rev.* **1989,** *89* (1), 165-198.

49. Hamilton, J. G.; Palke, W. E., Bonding in cyclopropane. *J. Am. Chem. Soc.* **1993,** *115* (10), 4159-4164.

50. de Meijere, A., Bonding Properties of Cyclopropane and Their Chemical Consequences. *Angew. Chem. Int. Ed.* **1979,** *18* (11), 809-826.

51. Dewar, M. J. S., Chemical implications of .sigma. conjugation. *J. Am. Chem. Soc.* **1984,** *106* (3), 669-682.

52. Gomes, J. A. N. F.; Mallion, R. B., Aromaticity and Ring Currents. *Chem. Rev.* **2001,** *101* (5), 1349-1384.

53. Wu, W.; Ma, B.; I-Chia Wu, J.; Schleyer, P. v. R.; Mo, Y., Is Cyclopropane Really the σ-Aromatic Paradigm? *Chem. Eur. J.* **2009,** *15* (38), 9730-9736.

54. Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B., Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003,** *103* (4), 977-1050.

55. Charette, A. B.; Beauchemin, A., Simmons-Smith Cyclopropanation Reaction. In *Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

56. Davies, H. M. L.; Antoulinakis, E. G., Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations. In *Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

57. Wong, F. M.; Wang, J.; Hengge, A. C.; Wu, W., Mechanism of Rhodium-Catalyzed Carbene Formation from Diazo Compounds. *Org. Lett.* **2007,** *9* (9), 1663-1665.

58. González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M., Rhodium-Catalyzed Cyclopropanation of Alkenes with Dimethyl Diazomalonate. *Adv. Synth. Catal.* **2008,** *350* (6), 813-816.

59. (a) Branca, S. J.; Lock, R. L.; Smith Iii, A. B., Exploitation of the vinylogous Wolff rearrangement. An efficient total synthesis of (±)-mayurone,(±)-thujopsene, and (.+-.)-thujopsadiene. *J. Org. Chem.* **1977,** *42* (19), 3165-3168; (b) McMurry, J. E.; Blaszczak, L. C., New method for the synthesis of enones. Total synthesis of (+-)-mayurone and (+-)-thujopsadiene. *J. Org. Chem.* **1974,** *39* (15), 2217-2222; (c) Mori, K.; Ohki, M.; Kobayashi, A.; Matsui, M., Synthesis of mono- and sesquiterpenoids—III : (±)-Thujopsene. *Tetrahedron* **1970,** *26* (11), 2815-2819; (d) Srikrishna, A.; Anebouselvy, K., An Enantiospecific Approach to Tricyclic Sesquiterpenes Mayurone and Thujopsenes1. *J. Org. Chem.* **2001,** *66* (21), 7102-7106.

60. Tang, Y.; Chi, Z.-F.; Huang, Y.-Z.; Dai, L.-X.; Yu, Y.-H., Highly stereoselective synthesis of vinyl and ethynylcyclopropane 1,1-dicarboxylic esters via semi-stabilized telluronium ylides. *Tetrahedron* **1996,** *52* (26), 8747-8754.

61. Baldwin, J. E., Thermal Rearrangements of Vinylcyclopropanes to Cyclopentenes. *Chem. Rev.* **2003,** *103* (4), 1197-1212.

62. Woodward, R. B.; Hoffmann, R., The Conservation of Orbital Symmetry. *Angew. Chem. Int. Ed.* **1969,** *8* (11), 781-853.

63. Tu-Hsin, Y.; Paquette, L. A., Silicon in organic synthesis. 16. A short synthesis of (+±)-α-vetispirene. *Tetrahedron Lett.* **1982,** *23* (32), 3227-3230.

64. Trost, B. M.; Nishimura, Y.; Yamamoto, K., A total synthesis of aphidicolin. *J. Am. Chem. Soc.* **1979,** *101* (5), 1328-1330.

65. (a) Carson, C. A.; Kerr, M. A., Heterocycles from cyclopropanes: applications in natural product synthesis. *Chem. Soc. Rev.* **2009,** *38* (11), 3051-3060; (b) Zhang, D.;

Song, H.; Qin, Y., Total Synthesis of Indoline Alkaloids: A Cyclopropanation Strategy. *Acc. Chem. Res.* **2011,** *44* (6), 447-457.

66. (a) Reissig, H.-U.; Zimmer, R., Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003,** *103* (4), 1151-1196; (b) Schneider, T. F.; Werz, D. B., Ring-Enlargement Reactions of Donor−Acceptor-Substituted Cyclopropanes: Which Combinations are Most Efficient? *Org. Lett.* **2011,** *13* (7), 1848-1851.

67. (a) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J., Catalytic Formal Homo-Nazarov Cyclization. *Org. Lett.* **2009,** *11* (4), 1023-1026; (b) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J., Formal Homo-Nazarov and Other Cyclization Reactions of Activated Cyclopropanes. *Chem. Eur. J.* **2011,** *17* (51), 14527-14538; (c) Murphy, W. S.; Wattanasin, S., A new cyclisation involving cyclopropyl ketones. A short route to 1-aryltetralones. *Tetrahedron Lett.* **1980,** *21* (19), 1887-1890; (d) Cavitt, M. A.; Phun, L. H.; France, S., Intramolecular donor-acceptor cyclopropane ring-opening cyclizations. *Chem. Soc. Rev.* **2014,** *43* (3), 804-818.

68. (a) Yu, M.; Pagenkopf, B. L., Formal [3 + 2] Cycloadditions of Donor−Acceptor Cyclopropanes and Nitriles. *J. Am. Chem. Soc.* **2003,** *125* (27), 8122-8123; (b) Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y., Highly Diastereoselective Construction of Fused Carbocycles from Cyclopropane-1,1-dicarboxylates and Cyclic Enol Silyl Ethers: Scope, Mechanism, and Origin of Diastereoselectivity. *Chem. Eur. J.* **2012,** *18* (8), 2196-2201; (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S., Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate

Ion Pair Pathway. *J. Am. Chem. Soc.* **2008,** *130* (27), 8642-8650; (d) Pohlhaus, P. D.; Johnson, J. S., Enantiospecific Sn (II)-and Sn (IV)-catalyzed cycloadditions of aldehydes and donor-acceptor cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (46), 16014-16015; (e) Pohlhaus, P. D.; Johnson, J. S., Enantiospecific Sn(II)- and Sn(IV)-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (46), 16014-16015.

69. (a) Lifchits, O.; Charette, A. B., A Mild Procedure for the Lewis Acid-Catalyzed Ring-Opening of Activated Cyclopropanes with Amine Nucleophiles. *Org. Lett.* **2008,** *10* (13), 2809-2812; (b) Wales, S. M.; Walker, M. M.; Johnson, J. S., Asymmetric Synthesis of Indole Homo-Michael Adducts via Dynamic Kinetic Friedel–Crafts Alkylation with Cyclopropanes. *Org. Lett.* **2013,** *15* (10), 2558-2561.

70. Schneider, T. F.; Kaschel, J.; Werz, D. B., A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2014,** *53* (22), 5504-5523.

71. Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B., Nucleophilic Addition of Phenol Derivatives to Methyl 1-Nitrocyclopropanecarboxylates. *J. Org. Chem.* **2008,** *73* (17), 6838-6840.

72. Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J., Polarity Inversion of Donor–Acceptor Cyclopropanes: Disubstituted δ-Lactones via Enantioselective Iridium Catalysis. *J. Am. Chem. Soc.* **2011,** *133* (46), 18618-18621.

73. Benfatti, F.; Nanteuil, F. d.; Waser, J., Iron-Catalyzed [3 + 2] Annulation of Aminocyclopropanes with Aldehydes: Stereoselective Synthesis of Aminotetrahydrofurans. *Org. Lett.* **2012,** *14* (1), 386-389.

74. Zhu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z., Lewis Acid Catalyzed Formal Intramolecular [3+2] Cross-Cycloaddition of Cyclopropane 1,1-Diesters with Alkenes: General and Efficient Strategy for Construction of Bridged [n.2.1] Carbocyclic Skeletons. *Angew. Chem. Int. Ed.* **2013,** *52* (7), 2032-2037.

75. Haubenreisser, S.; Hensenne, P.; Schröder, S.; Niggemann, M., The Alkynyl Moiety as a Donor for Donor–Acceptor Cyclopropanes. *Org. Lett.* **2013,** *15* (9), 2262-2265.

76. Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y., Ruthenium-Triggered Ring Opening of Ethynylcyclopropanes: [3+2] Cycloaddition with Aldehydes and Aldimines Involving Metal Allenylidene Intermediates. *Angew. Chem. Int. Ed.* **2013,** *52* (6), 1758-1762.

77. Xing, S.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z., Lewis Acid Catalyzed Intramolecular [3+2] Cross-Cycloaddition of Donor–Acceptor Cyclopropanes with Carbonyls: A General Strategy for the Construction of Acetal[n.2.1] Skeletons. *Angew. Chem. Int. Ed.* **2011,** *50* (52), 12605-12609.

78. Xia, X.-F.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M., Lewis Acid-Catalyzed Intramolecular [3+2] Cycloaddition of Cyclopropane 1,1-Diesters with Alkynes for the Synthesis of Cyclopenta[c]chromene Skeletons. *Chem. Asian J.* **2012,** *7* (7), 1538-1541.

79. Jung, M. E.; Chang, J. J., Enantiospecific Formal Total Synthesis of (+)-Fawcettimine. *Org. Lett.* **2010,** *12* (13), 2962-2965.

80. Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A., Stereodivergent Methodology for the Synthesis of Complex Pyrrolidines. *J. Am. Chem. Soc.* **2008,** *130* (12), 4196-4201.

81. (a) Carson, C. A.; Kerr, M. A., Total Synthesis of FR901483. *Org. Lett.* **2009,** *11* (3), 777-779; (b) Leduc, A. B.; Kerr, M. A., Total Synthesis of (−)-Allosecurinine. *Angew. Chem. Int. Ed.* **2008,** *47* (41), 7945-7948.

82. Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Y., (3 + 3)-Cyclodimerization of Donor–Acceptor Cyclopropanes. Three Routes to Six-Membered Rings. *J. Org. Chem.* **2011,** *76* (21), 8852-8868.

83. (a) Young, I. S.; Kerr, M. A., A Homo [3+2] Dipolar Cycloaddition: The Reaction of Nitrones with Cyclopropanes. *Angew. Chem. Int. Ed.* **2003,** *42* (26), 3023-3026; (b) Young, I. S.; Kerr, M. A., Three-Component Homo 3 + 2 Dipolar Cycloaddition. A Diversity-Oriented Synthesis of Tetrahydro-1,2-oxazines and FR900482 Skeletal Congeners. *Org. Lett.* **2004,** *6* (1), 139-141; (c) Sibi, M. P.; Ma, Z.; Jasperse, C. P., Enantioselective Addition of Nitrones to Activated Cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (16), 5764-5765.

84. Braun, C. M.; Congdon, E. A.; Nolin, K. A., Diastereoselective 1,3-Dipolar Cycloaddition of Nitrones to Donor–Acceptor Cyclopropanes Catalyzed by a Calcium(II) Complex. *J. Org. Chem.* **2015,** *80* (3), 1979-1984.

85. Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P., Lewis Acid/Rhodium-Catalyzed Formal [3 + 3]-Cycloaddition of Enoldiazoacetates with Donor–Acceptor Cyclopropanes. *Org. Lett.* **2015,** *17* (14), 3568-3571.

86. (a) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F., TiCl4 Promoted Formal [3 + 3] Cycloaddition of Cyclopropane 1,1-Diesters with Azides: Synthesis of Highly Functionalized Triazinines and Azetidines. *Org. Lett.* **2014,** *16* (18), 4896-4899; (b) Fang, J.; Hu, B.; Ren, J.; Wang, Z. W., Sc (OTf) 3-Catalyzed Tandem [3+ 2]

Cycloaddition/Nucleophilic Ring-Opening Reaction of Cyclopropane 1, 1-Diesters with Azomethine Ylides. *Asian J. Chem.* **2011,** *23* (4), 1479.

87. Stork, G.; Marx, M., Six-membered rings via olefin participation in the opening of acylcyclopropanes. *J. Am. Chem. Soc.* **1969,** *91* (9), 2371-2373.

88. Corey, E. J.; Balanson, R. D., A simple synthesis of (±)-cedrene and (±)-cedrol using a synchronous double annulation process. *Tetrahedron Lett.* **1973,** *14* (34), 3153-3156.

89. Marino, J. P.; Long, J. K., New strategies for annulations: a highly convergent and stereoselective synthesis of an octahydronaphthalene synthon for dihydrocompactin. *J. Am. Chem. Soc.* **1988,** *110* (23), 7916-7917.

90. Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M., Total Synthesis of Prostaglandins F2α and E2 as the Naturally Occuring Forms. *J. Am. Chem. Soc.* **1970,** *92* (2), 397-398.

91. De Simone, F.; Gertsch, J.; Waser, J., Catalytic Selective Cyclizations of Aminocyclopropanes: Formal Synthesis of Aspidospermidine and Total Synthesis of Goniomitine. *Angew. Chem. Int. Ed.* **2010,** *49* (33), 5767-5770.

92. Wenkert, E.; Hudlicky, T., Synthesis of eburnamonine and dehydroaspidospermidine. *J. Org. Chem.* **1988,** *53* (9), 1953-1957.

93. (a) Egawa, T., Molecular structure and puckering potential function of cyclobutane studied by gas electron diffraction and infrared spectroscopy. *J. Chem. Phys.* **1987,** *86* (11), 6018-6026; (b) Laane, J., Origin of the ring-puckering potential energy function for four-membered rings and spiro compounds: a possibility for pseudorotation. *J. Phys. Chem.* **1991,** *95* (23), 9246-9249; (c) Wiberg, K. B., Bent bonds in organic

compounds. *Acc. Chem. Res.* **1996,** *29* (5), 229-234; (d) Cruz-Cabeza, A. J.; Liebeschuetz, J. W.; Allen, F. H., Systematic conformational bias in small-molecule crystal structures is rare and explicable. *CrystEngComm* **2012,** *14* (20), 6797-6811.

94. Bartell, L. S.; Andersen, B., Methylene rocking and minimum bond tortuosity in cyclobutane. *J. Chem. Soc., Chem. Commun.* **1973,** (20), 786-787.

95. Hoffmann, R.; Davidson, R. B., Valence orbitals of cyclobutane. *J. Am. Chem. Soc.* **1971,** *93* (22), 5699-5705.

96. Rappoport, Z.; Rappoport, Z., *The Chemistry of Cyclobutanes, Part 2*. John WileySons Ltd.: Chichester, UK, **2006**.

97. Moran, D.; Manoharan, M.; Heine, T.; Schleyer, P. v. R., σ-Antiaromaticity in Cyclobutane, Cubane, and Other Molecules with Saturated Four-Membered Rings†. *Org. Lett.* **2003,** *5* (1), 23-26.

98. (a) Lee-Ruff, E., Synthesis of Cyclobutanes. In *The Chemistry of Cyclobutanes*, John Wiley & Sons, Ltd: **2005**; pp 281-355; (b) Rappoport, Z.; Liebman, J. F., *The chemistry of cyclobutanes*. John Wiley & Sons: **2005**.

99. Loutfy, R. O.; Mayo, P. D., Primary Bond Formation in the Addition of Cyclopentenone to Chloroethylenes. *Can. J. Chem.* **1972,** *50* (21), 3465-3471.

100. (a) Schuster, D. I.; Lem, G.; Kaprinidis, N. A., New insights into an old mechanism: [2 + 2] photocycloaddition of enones to alkenes. *Chem. Rev.* **1993,** *93* (1), 3-22; (b) Du, J.; Yoon, T. P., Crossed intermolecular [2+ 2] cycloadditions of acyclic enones via visible light photocatalysis. *J. Am. Chem. Soc.* **2009,** *131* (41), 14604-14605.

101. (a) Hyatt John, A., Ketene cycloadditions. *Organic Reactions 45*, 159-646; (b) Lee-Ruff, E.; Mladenova, G., Enantiomerically Pure Cyclobutane Derivatives and Their Use in Organic Synthesis. *Chem. Rev.* **2003,** *103* (4), 1449-1484.

102. Pan, J.; Hanna, I.; Lallemand, J.-Y., Synthesis of chiral cyclobutane derivatives by tetrahydropyran ring-opening. *Tetrahedron Lett.* **1991,** *32* (51), 7543-7544.

103. Lee‐Ruff, E., Synthesis of cyclobutanes. *Patai's Chemistry of Functional Groups* **2007**.

104. Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P., Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.* **2008,** *130* (39), 12886-12887.

105. Meyers, A. I.; Tschantz, M. A.; Brengel, G. P., Asymmetric Lewis Acid-Catalyzed Addition of a Ketene Dithioacetal to a Chiral Bicyclic Lactam. Formation of Cyclobutanopyrrolidinones. A New Class of GABA Derivatives. *J. Org. Chem.* **1995,** *60* (14), 4359-4362.

106. Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A., Carbocyclic thromboxane A2. *J. Am. Chem. Soc.* **1980,** *102* (4), 1404-1409.

107. Faure, S.; Piva-Le Blanc, S.; Piva, O., Synthesis of vinyl spirolactones and lactams by sequential cross-coupling metathesis, [2+2] photocycloaddition and cyclobutane ring-opening. *Tetrahedron Lett.* **1999,** *40* (33), 6001-6004.

108. Crimmins, M. T.; Gould, L. D., Intramolecular photocycloaddition-cyclobutane fragmentation: total synthesis of (±)-laurenene. *J. Am. Chem. Soc.* **1987,** *109* (20), 6199-6200.

109. Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K., Ring Contraction of Cyclobutanes and a Novel Cascade Reaction: Application to Synthesis of (±)-Anthoplalone and (±)-Lepidozene. *J. Org. Chem.* **1994,** *59* (26), 8092-8100.

110. Ghera, E.; Maurya, R., Synthesis and chemical transformations of cyclobuta[a]naphthalene and -anthracene derivatives. *Tetrahedron Lett.* **1987,** *28* (6), 709-712.

111. Namyslo, J. C.; Kaufmann, D. E., The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* **2003,** *103* (4), 1485-1538.

112. Reissig, H.-U.; Zimmer, R., Thrilling Strain! Donor–Acceptor-Substituted Cyclobutanes for the Synthesis of (Hetero)Cyclic Compounds. *Angew. Chem. Int. Ed.* **2015,** *54* (17), 5009-5011.

113. de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J., Cyclization and annulation reactions of nitrogen-substituted cyclopropanes and cyclobutanes. *Chem. Commun.* **2014,** *50* (75), 10912-10928.

114. Matsuo, J.-i., 1,4-Zwitterionic intermediates formed by cleavage of a cyclobutane ring and their cycloaddition reactions. *Tetrahedron Lett.* **2014,** *55* (16), 2589-2595.

115. Vemula, N.; Stevens, A. C.; Schon, T. B.; Pagenkopf, B. L., The [4+2] cycloaddition of donor-acceptor cyclobutanes and nitrosoarenes. *Chem. Commun.* **2014,** *50* (14), 1668-1670.

116. Stevens, A. C.; Palmer, C.; Pagenkopf, B. L., The Formal [4+3] Cycloaddition between Donor−Acceptor Cyclobutanes and Nitrones. *Org. Lett.* **2011,** *13* (6), 1528-1531.

117. Parsons, A. T.; Johnson, J. S., Formal [4 + 2] Cycloaddition of Donor−Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans. *J. Am. Chem. Soc.* **2009,** *131* (40), 14202-14203.

118. Machin Ben, P., BF_3•OEt_2-catalyzed reaction of donor-acceptor cyclobutanes with terminal alkynes: single-step access to 2,3-dihydrooxepines. *Synlett* **2011,** (19), 2799-2802.

119. Brimioulle, R.; Bach, T., [2+2] Photocycloaddition of 3-Alkenyloxy-2-cycloalkenones: Enantioselective Lewis Acid Catalysis and Ring Expansion. *Angew. Chem. Int. Ed.* **2014,** *53* (47), 12921-12924.

CHAPTER 2 NOVEL INTERRUPTED HOMO-NAZAROV CYCLIZATIONS[†,‡,1]

2.1 Oxyallyl Cations: Chemical Transformations and Synthetic Utility

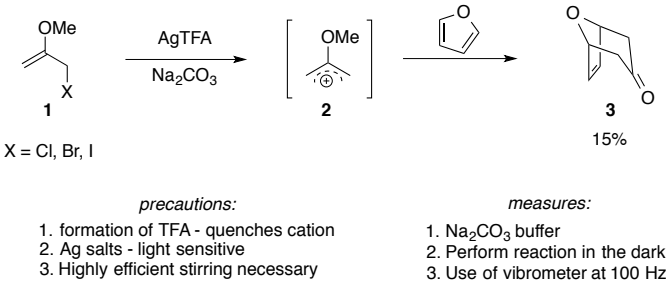
Oxyallyl cations have become a famously versatile class of electrophilic reactive intermediates. Early examples of the utilization of these intermediates in reactions involved simple systems, such as 2-methoxyallyl cation **2**, and their subsequent reactivity with dienes to afford bicyclic ketones, such as **3** (Scheme 2.1).[2] In this case, oxyallyl cation **2** is generated via a Ag-mediated ionization of a halo-substituted enol ether **1** accompanied by a concomitant precipitation of a Ag-based salt. Despite this important example, it took much effort and many years before oxyallyl cations gained traction as viable and reliable gateways to molecular complexity. Most of this time and effort was dedicated to designing conditions that prohibited their polymerizations and side reactions as well as identifying appropriate and effective synthetic precursors. Indeed, early investigations revealed oxyallyl cations to be elusive intermediates with high degrees of sensitivity towards order of addition of reagents, time-span for their additions, pH, and rate of stirring among other subtleties (Scheme 2.1).[2-3] It would take decades until the

---

[†] Work on allylsilane interrupted homo-Nazarov cyclization with Corey W. Williams and Katherine M. Francois. Published in *Org. Lett*. **2014**, *16*, 6468.

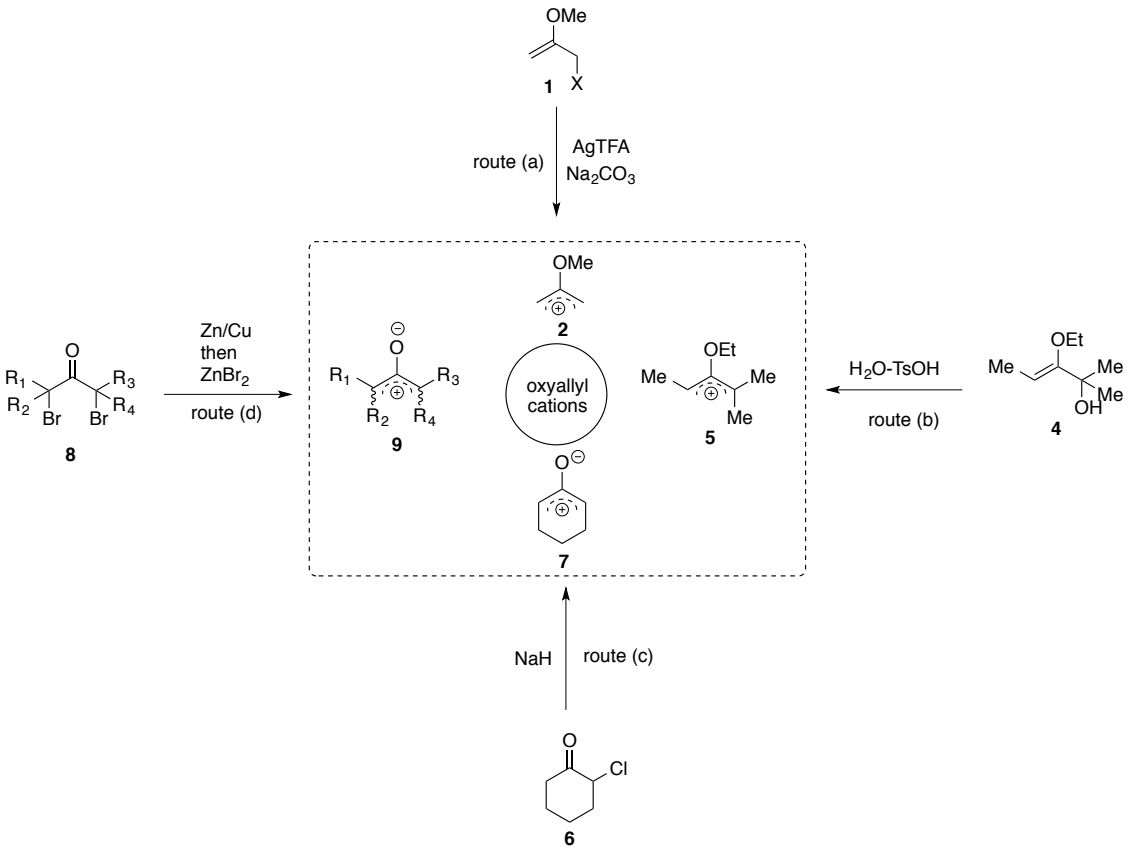
[‡] Work on arylative interrupted homo-Nazarov reactions done in collaboration with Corey W. Williams. Manuscript submitted for publication.

field of oxyallyl cation reactivity evolved enough to render them versatile, "go-to" intermediates for chemical synthesis.



Scheme 2.1. Early Oxyallyl Cation Synthesis.

Several generalized methods for synthesizing oxyallyl cation have become available.[4] As has been discussed, one method is through heterolysis of ally halides such as **1** (Scheme 2.2, route (a)). This method, perhaps the most concise of way for oxyallyl cation synthesis, typically utilizes Ag salts as the ionizing agent. A second method involves the activation of allyl alcohols of the type **2** under Brønsted acid conditions (Scheme 2.2, route (b)). Here, an acid-mediated E1 elimination affords the desired oxyallyl cations **5**. On the other hand, kinetic enolization of ketone **6** followed by heterolysis ensures cyclic oxyallyl cation **7** (Scheme 2.2, route (c)). Finally, reduction of α, α'-dihaloketones **8** using a Zn/Cu mixture affords enolates that can undergo ionization to form oxyallyl cations **9** (Scheme 2.2, route (d)). The development of these methods, among others, enabled efficient and reliable synthesis of oxyallyl cations.[2, 4-5] Consequently, their adoption into mainstream synthetic chemistry followed.

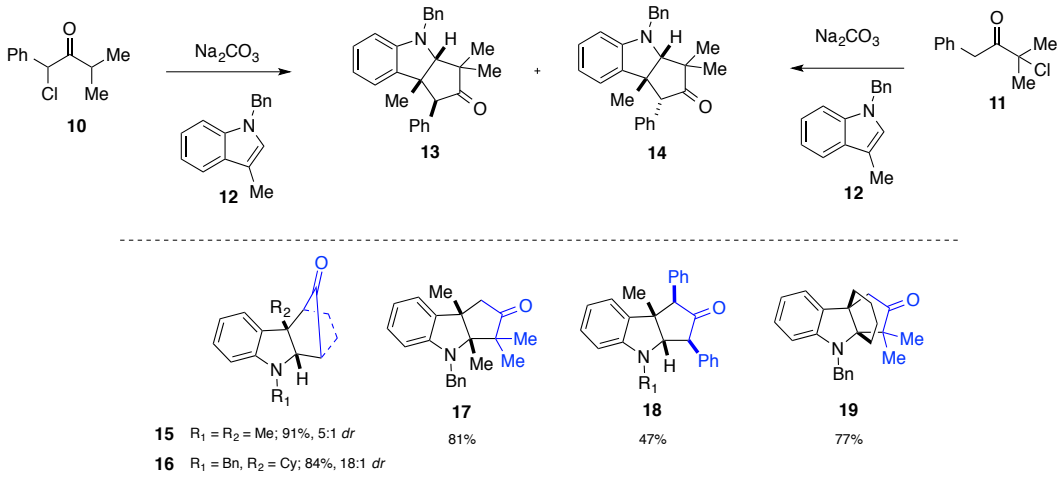


Scheme 2.2. Methods of Sythesizing Oxyallyl Cations.

Oxyallyl cations are electrophilic in nature and participate in an immensely diverse set of reactions with nucleophiles. Additionally, strategic substituents about oxyallyl cations can induce polarization of the positive charge distribution enabling regioselectivity and regiospecificity. Some highlight reactions involving oxyallyl cations are: [3+2]-cycloadditions, [4+3]-cycloadditions, Favorskii transformations.[5]

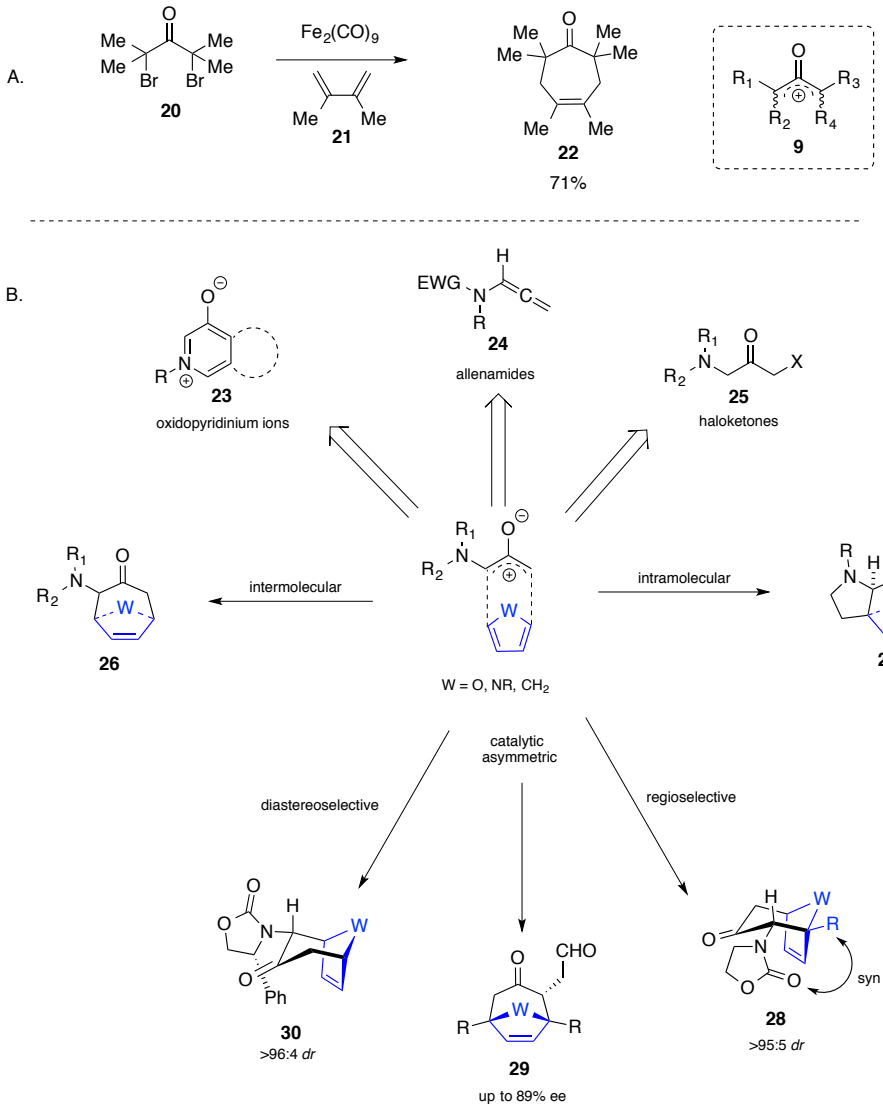
In the presence of electron-rich aromatics, oxyallyl cations derived from ketones **10** and **11** can undergo efficient [3+2]-cycloadditions (Scheme 2.3).[6] This reaction is a dearomative transformation and furnishes fused indolines, which are common structural motifs in indole alkaloid natural products. Interestingly, both 1- and 3-chlorosubstituted ketones **10** and **11** afford the same oxyallyl cation leading to the same indolines **13** and

14, albeit with different diastereoselectivities. A variety of fused indolines **15-19** are accessible using this transformation since this [3+2]-cycloaddition tolerates diverse cyclic and acyclic ketones.



Scheme 2.3. Dearomative [3+2]-Cycloadditions of Oxyallyl Cations.

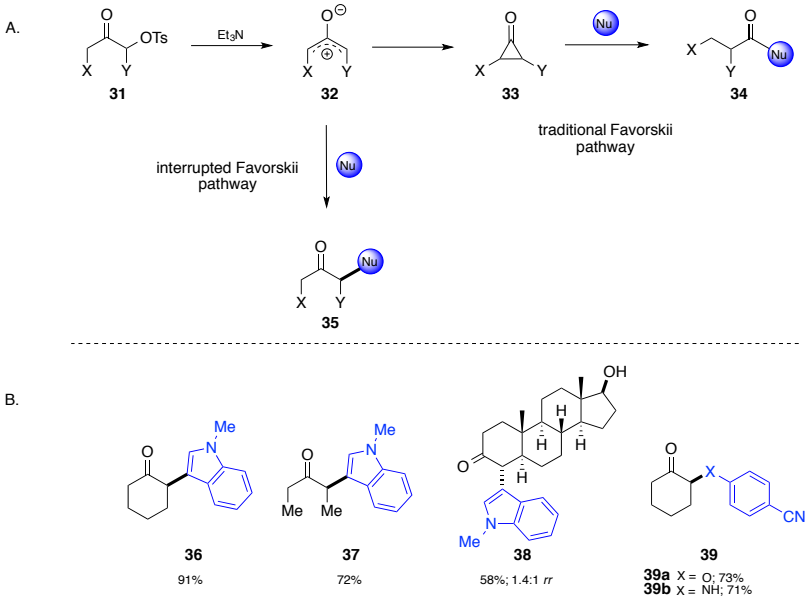
When subjected to electron-rich dienes such as **21**, oxyallyl cations **9** undergo [4+3]-cycloadditions to yield substituted cycloheptenones **22** (Scheme 2.4, A).[6a, 7] Other interesting [4+3]-cycloadditions involve nitrogen-stabilized oxyallyl cations derived from oxidopyridinium ions **23**, allenamides **24**, or aminohaloketones **25** (Scheme 2.4, B). Reactions of such oxyallyl cations with heteroaromatics provide entry into nitrogen-based bicyclic ketones via inter- and intramolecular transformations and in a diastereoselective, regioselective and catalytic asymmetric fashion (Scheme 2.4, B).



Scheme 2.4. [4+3]-Cycloadditions of Oxyallyl Cations.

The existence of transient oxyallyl cations **32** has been invoked in the traditional Favorskii reaction *en route* to cyclopropanones **33** (Scheme 2.5, A).[8] Subsequent ring-opening and rearrangement of cyclopropanones **33** in the presence of nucleophiles then affords functionalized carbonyls **34**. On the other hand, recently, it has been shown that interception of oxyallyl cations **32** with nucleophiles, such as indoles, leads to the formation of α-arylated ketones **36-38** in good yields (Scheme 2.5, B). This interception

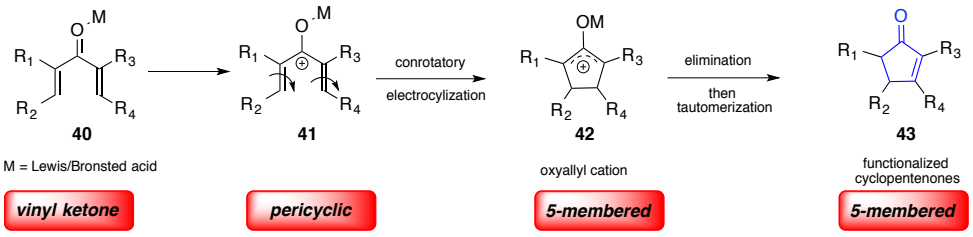
is a Friedel-Crafts-type transformation in nature. Heteroatoms can also serve as effective cation-trapping agents to afford ethers and amines **39**.



Scheme 2.5. The Interrupted Favorskii Reaction.

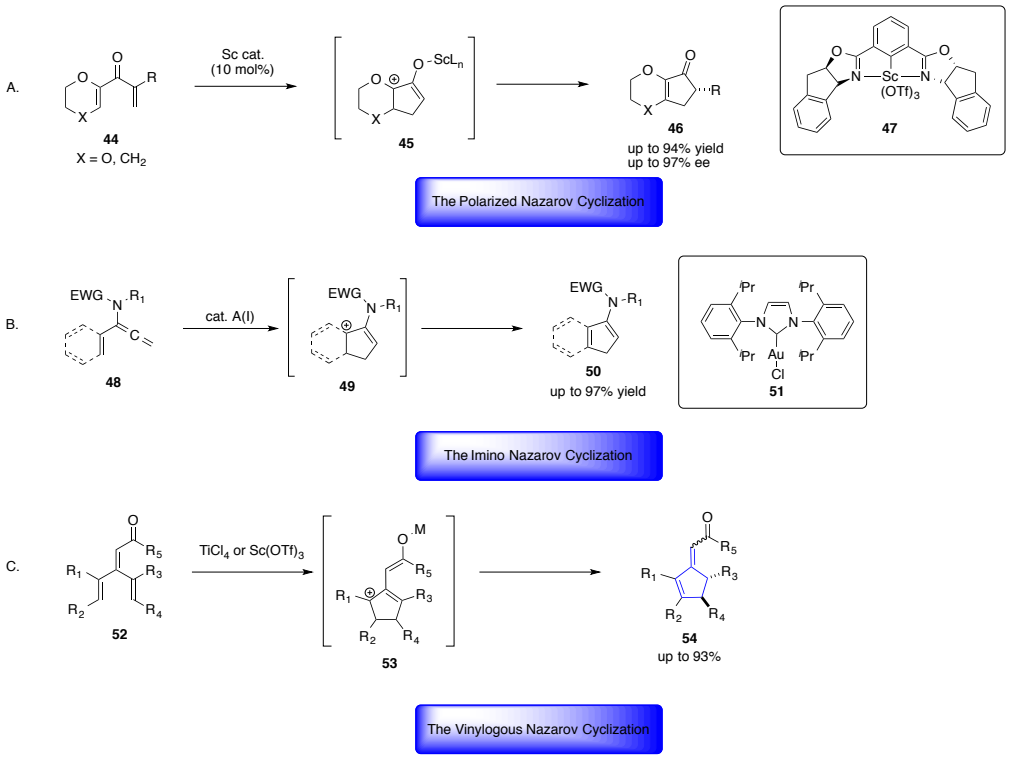
2.2 Oxyallyl Cations in Nazarov and Homo-Nazarov Cyclizations

Oxyallyl cations have been extensively studied in the Nazarov[9] and homo-Nazarov[10] cyclizations. In the Nazarov reaction, divinyl ketones **40** undergo activation followed by conrotatory 4π electrocyclizations to form cyclic oxyallyl cations **42** (Scheme 2.6). Both Lewis and Brønsted acids are viable activators for this transformation. Oxyallyl cations **42** then undergo subsequent E1 elimination then tautomerization to afford functionalized cyclopentenones **43**.



Scheme 2.6. The Nazarov Cyclization.

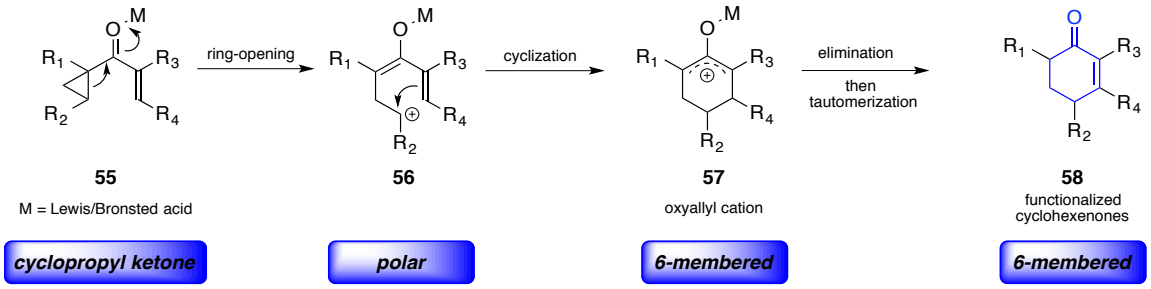
Several variations of the Nazarov cyclization exist (Scheme 2.7). In "polarized" Nazarov reactions, the presence of heteroatoms, as in the enol ether moiety of **44**, improves the overall selectivity in the reaction.[11] This selectivity is a consequence of biasing of the positive charge in the subsequent oxyallyl cations resulting in the exclusive formation of tetrasubstituted alkenes **46** in high yields (Scheme 2.7, A). Upon subjection to the chiral Sc-based ligand **47**, highly asymmetric proton transfer affords resulting cyclopentenones **46** in exceptional enantioselectivity. Another variant, the "imino-Nazarov" cyclization utilizes allenamide precursors **48** that, in the presence of appropriate Lewis acid activation, such Au salt **51**, undergo electrocyclization to afford a variety of fused cyclopentenamides **50** (Scheme 2.7, B).[12] Imino-Nazarov reactions are synthetically useful transformations and allow access into alkaloid-type molecular scaffolds. Additionally, formation of oxyallyl cations is possible with conjugated trienes **52** through activation by Lewis acids such as $TiCl_4$ or $Sc(OTf)_3$ (Scheme 2.7, C).[13] Cyclization of the resulting oxyallyl cations can then furnish dienones **54**. This variant is known as the "vinylogous" Nazarov cyclization. Much effort has been dedicated to investigating the Nazarov reaction, and as a result, this transformation is well studied. As a result, the synthetic utility of the Nazarov cyclization has been showcased by its use in numerous total syntheses of natural products.[14]



Scheme 2.7. Variations of the Nazarov Cyclization.

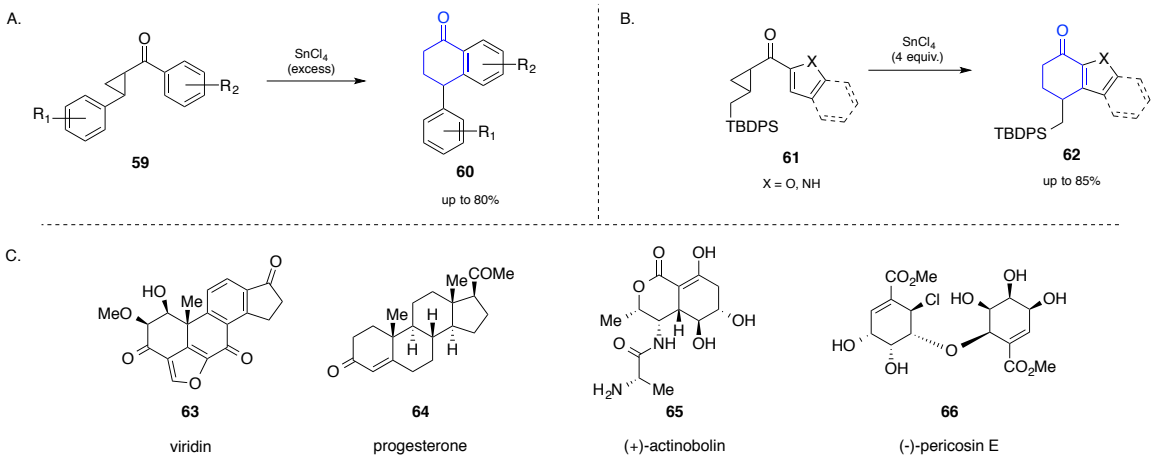
Replacing one the vinyl groups in the divinyl ketones in Nazarov reactions affords cyclopropyl vinyl ketones **55**, substrates that can undergo polar, stepwise intramolecular ring-opening cyclizations upon acid activation (Scheme 2.8).[15] The products of these ring-opening cyclizations are 6-membered oxyallyl cations **57** that can then eliminate and tautomerize to furnish cyclohexenones **58**. This transformation from cyclopropyl vinyl ketones **55** to cyclohexanones **58** is known as the homo-Nazarov cyclization, and is homologous to the traditional Nazarov reaction. Unlike its parent Nazarov reaction, the homo-Nazarov cyclization has only recently been realized and is relatively much less studied. It is important to note another significant difference between the formation oxyallyl cations in the two transformations: Nazarov reactions include oxyallyl cation

formation via a pericyclic electrocyclization pathway whereas stepwise, ring-opening/cyclizations afford oxyallyl cations in the homo-Nazarov variant.



Scheme 2.8. The Homo-Nazarov Cyclization.

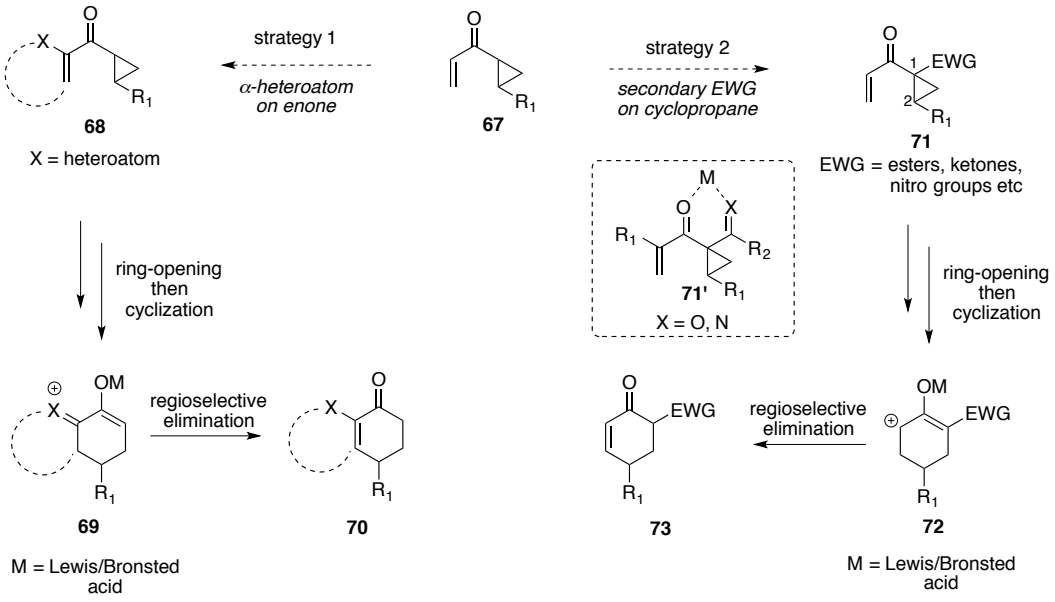
Traditional examples of the homo-Nazarov cyclization involved the use stoichiometric amounts of Lewis/Brønsted acids and/or elevated reaction temperatures. Typical metal salts such as $SnCl_4$ effect the transformation and afford variously fused cyclohexenone molecular scaffolds **60** and **62** (Scheme 2.9, A and B).[16] Aryl- and heteroaryl-fused cyclohexanones **60** and **62** are thus obtained in good yields. These early examples of homo-Nazarov cyclizations demonstrated the potential of this transformation for the synthesis of interesting scaffolds. Natural products bearing fused cyclohexenone and cyclohexenol moieties are prevalent. Representative examples of such natural products, which have also received much attention from synthetic chemists, include viridin (**64**),[17] progesterone (**64**),[18] (+)-actinobolin (**65**),[19] and (-)-percosin E (**66**)[20] among numerous others (Scheme 2.9, C).



Scheme 2.9. Examples and Utility of Homo-Nazarov Cyclizations.

Use of stoichiometric amounts of the toxic $SnCl_4$ was an obvious synthetically unappealing feature of early homo-Nazarov cyclizations. Through judicious scouting of the reaction conditions and viable substrates, synthetic chemists later devised several strategies for achieving catalysis within this transformation.[15a, 21] The first strategy involves utilization of α-heteroatoms on the enone moiety, an alteration that renders the π-system more nucleophilic, thus facilitating ring opening (Scheme 2.10). Due to the enhanced reactivity of the enone **68**, a decreased amount of the acid promoter is typically needed to effect the ring-opening cyclization thus enabling catalysis. A further consequence of this strategy is regioselective elimination leading to the exclusive formation of cyclohexenone **70**. The oxyallyl cation intermediate formed upon ring-opening cyclization, **69**, is stabilized and polarized by the α-heteroatom and as a result, exclusive elimination of leads to cyclohexenone **70**. On the other hand, the second strategy involves the use of secondary electron withdrawing groups (EWGs) of the cyclopropane (Scheme 2.10). The resulting cyclopropanes **71**, bearing one donor and two acceptor groups are classified as donor-acceptor-acceptor (D-A-A) cyclopropanes.

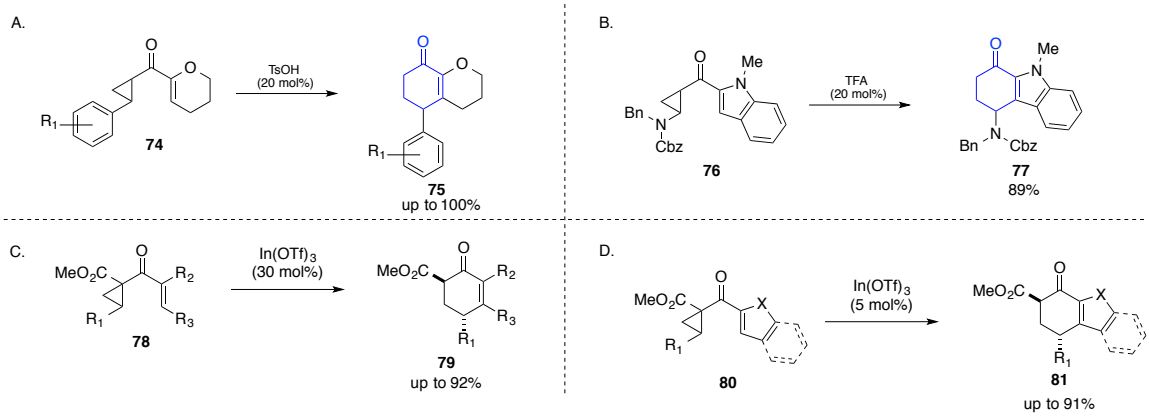
Having a secondary EWG leads to further weakening of the C(1)-C(2) bond, allowing ring-opening to occur under milder catalytic conditions. In cases where the EWG has lone pairs, bidentate binding of the acid promoter onto the cyclopropane is possible via a putative 6-membered chelate **71'**. This doubly-bound complex can potentially allow for more effective C(1)-C(2) bond weakening hence catalysis. Additionally, once oxyallyl cation **72** is formed, a majority of charge is polarized onto the carbon distal to the EWG thus allowing for regioselective elimination. This elimination then leads to exclusive formation of cyclohexenones **73**. Overall, these two strategies for attaining catalysis in the homo-Nazarov cylization are complementary and allow entry into regioselective synthesis of potential natural product-like cores.



Scheme 2.10. Strategies for Catalysis in the Homo-Nazarov Cyclization.

As a demonstration of strategy 1 (Scheme 10), Bronsted acids (examples: TsOH and TFA, 20 mol% loading) were shown to be effective promoters for catalytic homo-Nazarov cyclizations of substrates bearing α-heteroatoms (Scheme 2.11, A and B).[15a, 15c]

These examples are some of the earliest demonstrations of effective catalysis in the homo-Nazarov reaction. Follow-up work using strategy 2, the D-A-A approach, also eventually led to successful catalysis (Scheme 2.11, C).[22] In this case, 30 mol% of $In(OTf)_3$ was sufficient to promote the synthesis of cyclohexenones **79** from D-A-A cyclopropanes **78**. Ultimately, combining these two strategies (α-heteroatom and secondary EWG) into one system afforded substrates such as cyclopropane **80**, which smoothly underwent homo-Nazarov cyclizations with catalyst loading as low as 5 mol% $In(OTf)_3$ (Scheme 2.11, D).[23] This establishment of such effective catalytic reaction conditions enabled the homo-Nazarov cyclization (and derivatives thereof) to gain traction as a viable and synthetically useful transformation for generating functionalized polycycles[24] and in the synthesis of natural products.[15a, 24d]

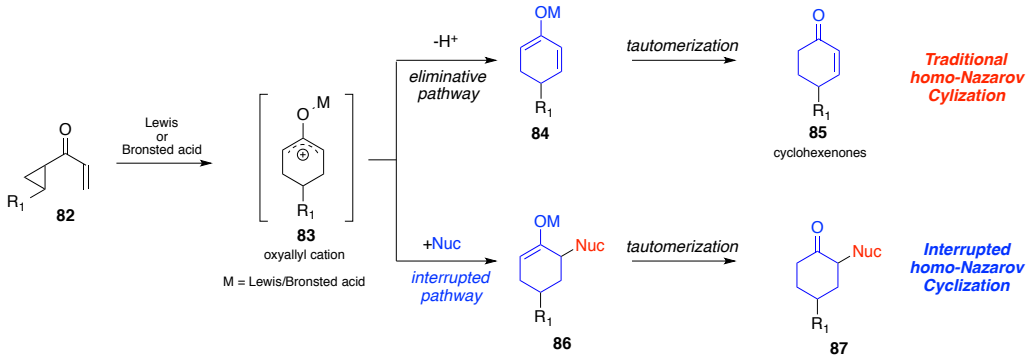


Scheme 2.11. Variations of Homo-Nazarov Cyclizations.

2.3 The Interrupted Homo-Nazarov Cyclization

As was highlighted earlier in this chapter, oxyallyl cations are impressively useful intermediates whose electrophilic nature allows them to react with a plethora of nucleophilic agents. The homo-Nazarov cyclization, being a transformation that goes through an intermediate oxyallyl cation, is a viable candidate for reactivity with

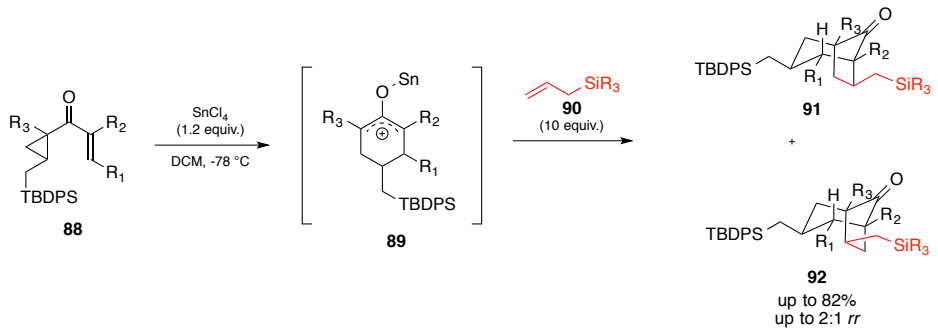
nucleophiles (Scheme 2.12). The nature of such reactivity is an interception of the oxyallyl cation intermediate with nucleophilic trapping agents and leads to preclusion of the elimination/tautomerization pathway. Such a transformation, known as the "interrupted homo-Nazarov" reaction leads to the formation of functionalized cyclohexanones (Scheme 2.12). It is noteworthy that similar interception of oxyallyl cations has been extensively demonstrated for interrupted Nazarov cyclizations using alkenes, arenes, heteroatoms and many other nucleophiles.[10, 14b, 25]



Scheme 2.12. Homo-Nazarov and Interrupted Homo-Nazarov Cyclizations.

Compared to the its interrupted Nazarov counterpart, the interrupted homo-Nazarov cyclization is much less studied. In 2014, a seminal report of the interrupted homo-Nazarov reaction was reported by Yadav and co-workers (Scheme 2.13).[26] Using stoichiometric amounts of $SnCl_4$ promoter, oxyallyl cations **89** are formed and undergo allylsilane-capture in a [3+2]-cycloaddition fashion. Bicyclic ketones of the type **91** and **92** were thus formed, as regioisomeric mixtures. It should be noted that as of 2014, to the best of our knowledge, this study was the only report of an attempt towards an interrupted homo-Nazarov cyclization. While pioneering, Yadav's study still suffered from significant limitations: (1) lack of regioselectivity; (2) narrow substrate scope; and (3) the requirement for stoichiometric amounts of toxic $SnCl_4$. As a result, a need existed for the

development of novel methodologies that would address these limitations as well as demonstrate the synthetic utility of the interrupted homo-Nazarov cyclization for broader synthetic applications.

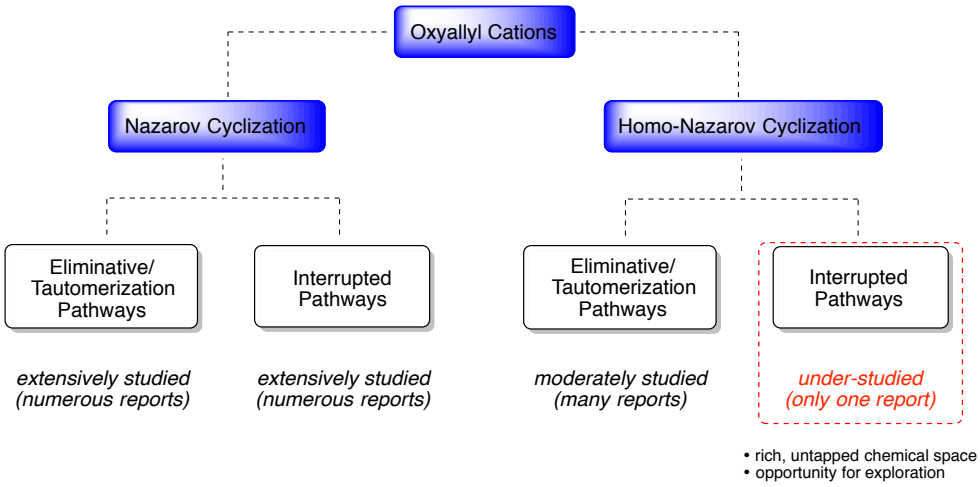


Scheme 2.13. Yadav's Interrupted Homo-Nazarov Cyclization.

2.4 Development of Catalytic, Chemodivergent, and Modular Interrupted Homo-Nazarov Cyclizations

As described in the previous sections, oxyallyl cations are important intermediates in Nazarov and homo-Nazarov reactions. The chemical landscape for these reactive intermediates reveals an imbalance in the amount of attention dedicated to variants of the Nazarov and homo-Nazarov cyclizations (Scheme 2.14). On one hand, uses of oxyallyl cations for synthesis of cyclopentenones (elimination/tautomerization pathway) and cyclopentanones (interrupted pathway) have been extensively studied and well documented (Scheme 2.14). On the other hand, the homo-Nazarov cyclization, being in its infancy, has received much less attention. A handful of literature reports of elimination/tautomerization pathways in the homo-Nazarov reactions exist. Notably, the interrupted variant to the homo-Nazarov cyclization has been severely understudied. In fact, only one example of this transformation was published as of 2014. This pioneering report, however, suffered from limitations in substrate scope, low selectivity and the need

for stoichiometric amount of a toxic Lewis acid promoter. Therefore, the development of generalizable, selective and catalytic interrupted homo-Nazarov cyclizations would be of immense benefit to the synthetic community.



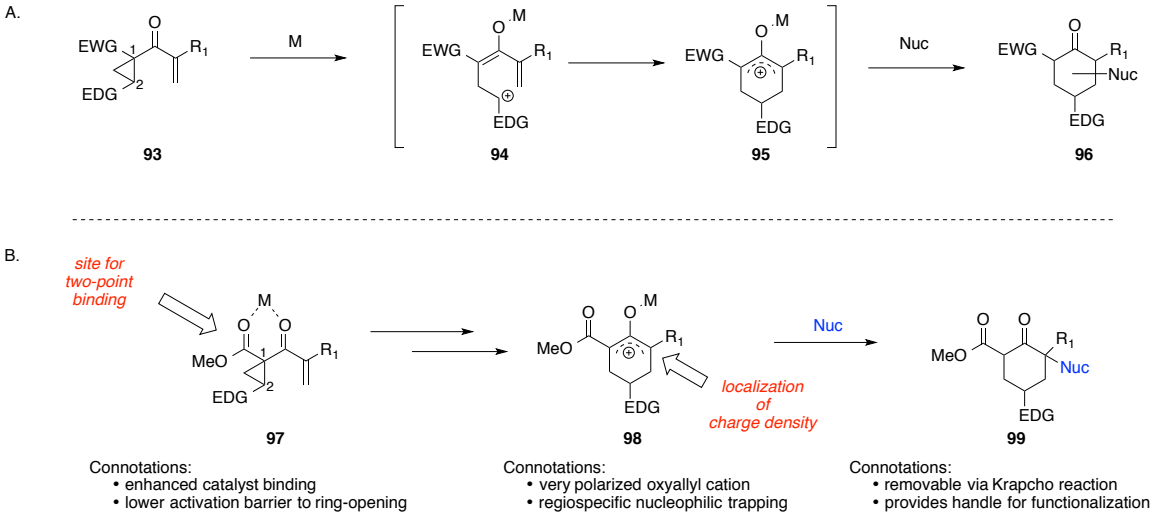
Scheme 2.14. Chemical Landscape for Nazarov and Homo-Nazarov Cyclizations.

2.5 An Allylative Interrupted Homo-Nazarov Cyclization

2.5.1 Reaction Design

In designing a model system for an effective interrupted homo-Nazarov process, various considerations had to be taken into account. As has been mentioned in previous sections, D-A-A cyclopropanes of the type **93** have been demonstrated to effective in ring-opening transformations (Scheme 2.15, A). As a result the choice of secondary electron withdrawing group (EWG) on the cyclopropane was key. The most effective EWG would have characteristics that would enable: (1) a site for binding with oxophilic Lewis acids enabling catalysis; (2) strong polarization of the oxyallyl cation intermediate to allow for regiospecific reactivity with nucleophiles (Scheme 2.15, B). Additionally, bonus features for a desirable EWG would include: (1) ease of installation on the cyclopropane starting material; (2) ease of removal in the cyclohexanone product; or (3)

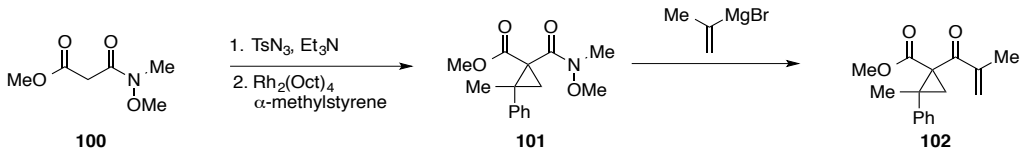
provision of a synthetic handle for further functionalization in the product. Given these guidelines, many potential EWGs were considered including esters, ketones, sulfones, sulfoxide, nitriles, and nitro groups, among others. In the end, simple esters seemed a good choice of an EWG as they fit virtually all of the guidelines proposed. It should be noted that esters have be shown to be beneficial EWGs for several Nazarov[14b] and homo-Nazarov[15a, 21] transformations as well.



Scheme 2.15. Strategy Towards a Catalytic Interrupted Homo-Nazarov Cyclization.

2.5.2 Synthesis of the Model Substrate

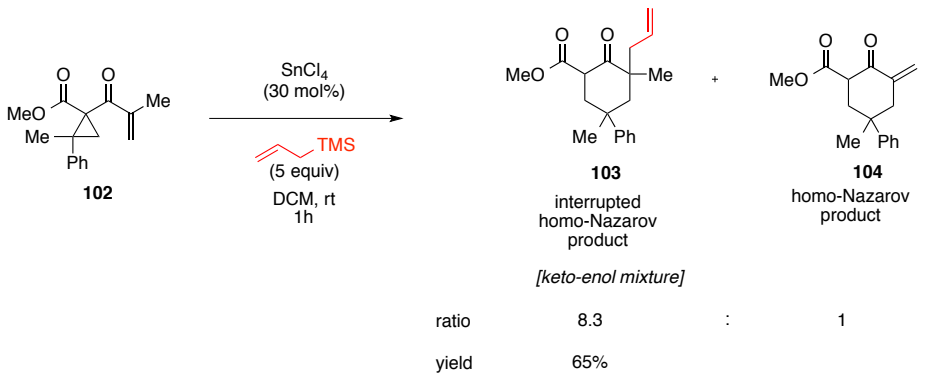
The model cyclopropane, **102**, for our efforts towards an interrupted homo-Nazarov cyclization was synthesized according to Scheme 2.16 in accordance with our lab's previously reported protocol.[22] This procedure involves an initial diazo transfer reaction on Weinreb amide ester **100**, followed by a Rh-catalyzed cyclopropanation to afford cyclopropane **101**. Subjecting cyclopropane **101** to isopropenylmagnesium bromide affords model cyclopropane **102**.



Scheme 2.16. Synthesis of Model D-A-A Cyclopropane.

2.5.3 Proof of Principle

Confident of our chances towards effective interrupted homo-Nazarov cyclizations, cyclopropane **102** was subjected to 30 mol% $SnCl_4$ in the presence of 5 equiv of allyl-TMS (Scheme 2.17). The choice of utilizing $SnCl_4$ as starting point for this transformation was based on specific reasoning: (1) $SnCl_4$ is both strongly Lewis acidic and highly oxophilic thus presumably suited our dicarbonyl cyclopropane substrate; (2) $SnCl_4$ tolerates simple allylsilanes which minimizes degradation pathways. Gratifyingly, the interrupted homo-Nazarov product **103** was observed under the stated catalytic conditions in 65% yield. This reaction, importantly, represents one of the first examples of an interrupted homo-Nazarov cyclization under catalytic conditions. Undesired exocyclic alkene **104**, the homo-Nazarov product, results from untrapped oxyallyl cation undergoing E1-elimination. While satisfactory, this reaction example still had several points of potential improvements: (1) lowering the $SnCl_4$ loading further than 30 mol% or identification of a suitable back-up catalyst; (2) increasing selectivity towards the desired product **103**; and (3) increasing chemical yield.



Scheme 2.17. A Catalytic, Interrupted Homo-Nazarov Cyclization.

2.5.4 Reaction Optimization

Having established the possibility of effective catalytic interrupted formal homo-Nazarov cyclization, an optimization process for this transformation was in order. A 30 mol% loading of $SnCl_4$ was an immediate concern, and so efforts to lower this catalyst loading were carried out (Table 2.1). Unfortunately, all attempts to lower the catalyst loading resulting in lowered yields. Interestingly, the selectivities towards the desired product appeared independent of amount of Lewis acid. Given this fact, a loading of 20 mol% was chosen to be a good compromise between chemical yield and acceptable loading of $SnCl_4$ (Table 2.1, entry 2).

Table 2.1. Catalyst Loading Optimization[a]

entry	$SnCl_4$ loading (mol%)	time (h)	yield of **103**[b] (%)	**103**: **104**[c]
1	30	1	51	1.9 : 1
2	20	24	42	2.2 : 1
3	15	24	32	2.1 : 1
4	10	48	24	2.3 : 1
5	5	48	16	2.8 : 1

[a] Reaction run with 1 equiv of **102** and 5 equiv of allyl-TMS at room temp in DCM (0.1 M). [b] Isolated yield after column chromatography. [c] Ratio determined by ^{1}H-NMR.

An investigation of alternate Lewis acids to $SnCl_4$ was carried out (Table 2.2). The choice of Lewis acid screened was based on the degree of oxophilicity as well as extent of Lewis acidity. Most of the catalysts screened were readily available triflate salts whose ligands readily dissociate from the metal center facilitating binding onto the cyclopropane substrates. Successful Lewis acids were chosen on the basis of chemical yield as well as selectivity towards the interrupted homo-Nazarov products. Interestingly, +3 Lewis acid salts tended to give interrupted homo-Nazarov product **103** in good to high selectivity (Table 2.2, entries 3, 4, 5). On the other hand, +2 salts afforded mostly homo-Nazarov product **104**, albeit in lowered yields (Table 2.2, entries 10, 11, 12, 13). $SnCl_4$ proved to be the most competent Lewis acid, both in terms of selectivity (17:1) and yield (75%) towards oxyallyl cation trapping (Table 2.2, entry 1).

Table 2.2. Lewis Acid Screen[a]

entry	Lewis acid	time (h)	yield of **103**[b] (%)	**103** : **104**[c]
1	$SnCl_4$	24	75	17 : 1
2	$TiCl_4$	96	34	1: 1.1
3	$In(OTf)_3$	2	41	1.7 : 1
4	$Sc(OTf)_3$	6	43	4.2 : 1
5	$Al(OTf)_3$	72	42	6.8 : 1
6	$Ga(OTf)_3$	70	12	1 : 1.3
7	$Yb(OTf)_3$	70	26	2.3 : 1
8	$InCl_3$	48	28	1 : 1.5
9	$BF_3 \bullet OEt_2$	70	34	1.1 : 1
10	$Sn(OTf)_2$	48	20	1 : 2.4
11	$Zn(OTf)_2$	48	13	1 : 2.3
12	$Cu(OTf)_2$	48	11	1 : 6.7
13	$Mg(OTf)_2$	48	9	1 : 4.2

[a] Reaction run with 1 equiv of **102**, 10 equiv of allyl-TMS, and 20 mol% Lewis acid at room temp in DCM (0.1 M). [b] Isolated yield after column chromatography. [c] Ratio determined by ^{1}H-NMR.

In an effort to circumvent the need to utilize $SnCl_4$ as a catalyst for this transformation, $In(OTf)_3$ was chosen as a candidate for further optimization (Table 2.3). We hoped these efforts would achieve a backup catalyst. An initial result had revealed 20 mol% $In(OTf)_3$ to afford 41% of product **103** (Table 2.3, entry 1). Lowering the loading of $In(OTf)_3$ to 5 mol% afforded interrupted product **103** in 63% and a 5.6:1 selectivity (Table 2.3, entry 4). This result demonstrates that catalysts other than $SnCl_4$ can potentially serve as backup catalysts for effecting the interrupted homo-Nazarov cyclization.

Table 2.3. Optimization of a Back-up Catalyst[a]

entry	$In(OTf)_3$ loading (mol%)	time (h)	yield of **103**[b] (%)	**103** : **104**[c]
1	20	2	41	1.7 : 1
2	15	3	49	4 : 1
3	10	5	43	2.7 : 1
4	5	19	63	5.6 : 1

[a] Reaction run with 1 equiv of **102** and 10 equiv of allyl-TMS at room temp in DCM (0.1 M). [b] Isolated yield after column chromatography. [c] Ratio determined by ^{1}H-NMR.

The effect of solvent on this transformation was then investigated. For this study, classes of solvents were systematically chosen based on polarity, coordinating ability, or hydrogen bonding capability (Table 2.4). Polar protic and aprotic solvents (MeOH, DMF, MeCN) caused the reaction to stall, and either starting material or intractable degradation products were recovered (Table 2.4, entries 1-3). THF and EtOAc also did not support the desired transformation (Table 2.4, entries 4-5). Presumably, these five solvents, being coordinating, sequestered the Lewis acid catalyst or altered its binding ability, thus preventing desired product formation. In contrast, non-polar and weakly coordinating solvents provided favorable reaction outcomes. Dichloromethane proved to be the

superior solvent, providing the highest chemical yield as well as selectivity towards the desired cyclohexenol **103** (Table 2.4, entry 9).

Table 2.4. Solvent Screen[a]

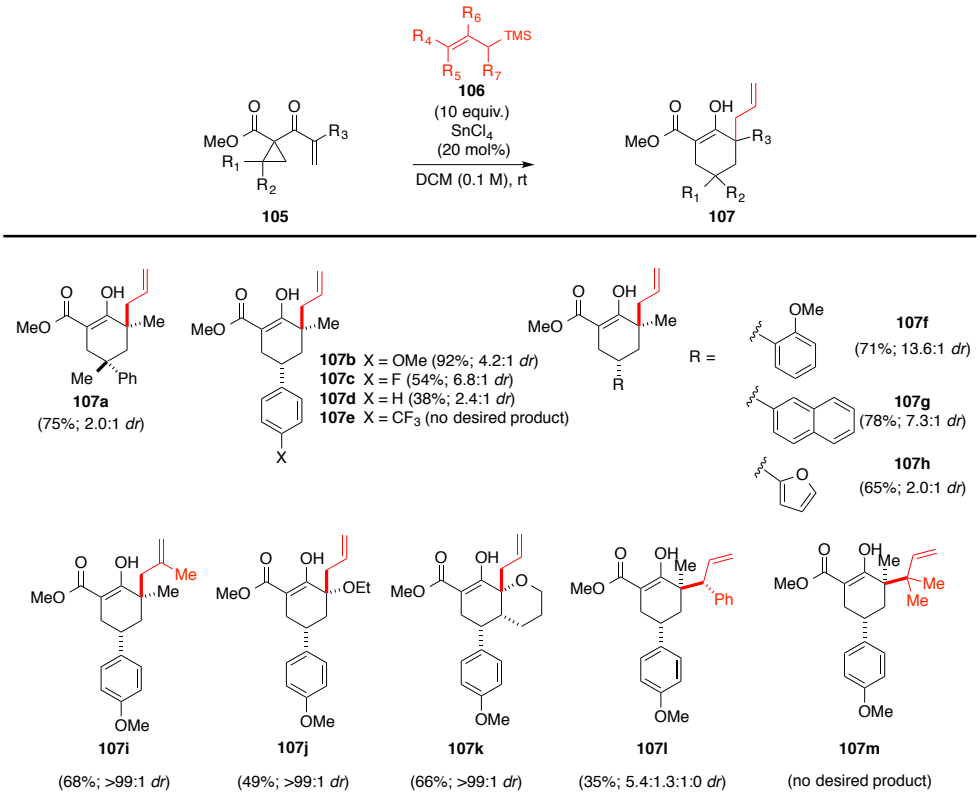
entry	Solvent	time (h)	yield of **103**[b] (%)	**103** : **104**[c]
1	MeOH	36	--[d]	--
2	DMF	36	--[d]	--
3	MeCN	10	--[d]	--
4	THF	72	--[d]	--
5	EtOAc	2	--[d]	--
6	1,2-DCE	6	63	6.5 : 1
7	Hexane	36	20	1.7 : 1
8	PhMe	36	36	2.3 : 1
9	DCM	24	75	17 : 1

[a] Reaction run with 1 equiv of **102** and 10 equiv of allyl-TMS at room temp in DCM (0.1 M) using 20 mol% $SnCl_4$. [b] Isolated yield after column chromatography. [c] Ratio determined by ^{1}H-NMR. [d] Decomposition and/or intractable side products observed.

2.5.5 Reaction Scope and Limitations

Armed with a set of optimized conditions (20 mol% $SnCl_4$, 10 equiv ally-TMS), DCM (0.1 M), exploration of the substrate scope in the interrupted homo-Nazarov cyclization was initiated (Scheme 2.18). Firstly, different functionalized cyclopropanes were studied using allyltrimethylsilane **106** as the nucleophilic trapping agent. Cyclopropanes bearing efficient, carbocation-stabilizing donor groups generally led to increased yields (**107a**, 75% yield; **107b**, 92% yield). This trend was also confirmed upon studying different para substituents on a phenyl donor group. A *para*-methoxy substituent afforded 92% yield whereas a *para*-fluoro group gave a 54% yield (**107c**). Unsubstituted phenyl donor afforded only a 38% yield (**107d**) while substitution with a strong electron-withdrawing group such as the 4-trifluoromethyl group (**107e**) did not afford any desired

product at all. These trends can be explained based on the proposed mechanism discussed previously. Good donor groups on the cyclopropane allow for efficient and rapid ring-opening due to carbocation stabilization on the benzylic position. This, in turn, affords the oxyallyl cation intermediates for subsequent trapping with the allylsilane nucleophile. Other good donor groups such as the 2-OMe-Ph-, 2Napthyl-, and 2-furyl groups are also effective and provided interrupted products **107f**, **107g**, and **107h** in 71%, 78%, and 65% yields respectively. Extending this study to enol-ether π-systems or alternate allylsilanes affords interrupted products **107j-107k** in modest to good yields. However, putting *gem*-dimethyl substituents on allyl-TMS did not afford desired cyclohexenol **107m** presumably due to steric clash upon nucleophile approach.



Scheme 2.18. Scope of the Catalytic, Interrupted Homo-Nazarov Cyclization.

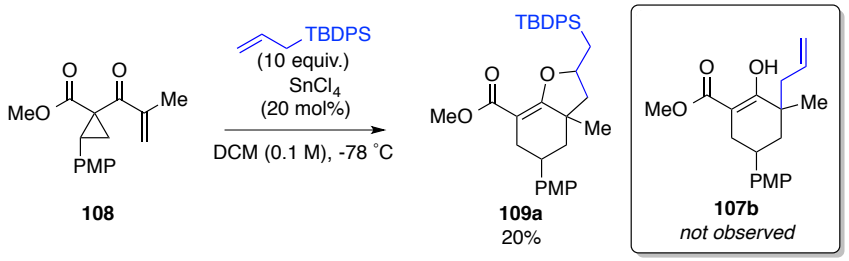
Interesting stereochemical outcomes were observed during this study. Since products were formed as diastereomeric as well as keto-enol mixtures, NMR interpretation was difficult. As a result, products formed were capped using TMSCl thus significantly simplifying the NMR spectra and allowing interpretation. All interrupted homo-Nazarov products were formed in a regiospecific fashion at the α'-carbon as planned (strong polarization of the intermediate oxyallyl cation due to the ester group). Also, products were formed with a *trans* configuration in the major diastereomers as a result of nucleophilic attack from a trajectory opposite that of the donor group. Perplexingly, while most of the substrates studied allowed modest to good diastereoselectivities, alkoxy-substituted cyclohexenols **107j** and **107k** were formed with complete distereoselection. The effect of the alkoxy group on the intermediate oxyallyl cation and its connotations in the transition state towards nucleophilic trapping remain a mystery and is yet to be fully determined.

2.6 A Chemodivergent, Interrupted Homo-Nazarov Cyclization

During the course of the study, it was observed that in the presence of bulky allylsilanes and at lowered temperatures, such as allyl-TBDPS, the previously obtained allylated cyclohexenols **107b** were not observed (Scheme 2.19, A). Instead, hexahydrobenzofurans **109a** were obtained. This interesting chemodivergence is a result of an unexpected and highly unusual formal [3+2]-cycloaddition that had not been reported before in the homo-Nazarov cyclization. This, in turn, prompted a further investigation (Scheme 2.19, B). Unfortunately, this study revealed the necessity for stoichiometric amounts of $SnCl_4$ for the synthesis of hexahydrobenzofuran **109a** (Scheme

2.19, B). All attempts to lower the loading of $SnCl_4$ as well as use of other Lewis acids led either to significantly reduced yields or degradation products.

A.



B.

entry	Loading (mol%)	Conc. (M)	time (h)	yield of **109a**[b] (%)
1	20	0.1	3	20
2	20	0.05	1	33
3	20	0.01	1	41
4	50	0.01	1	49
5	120	0.01	1	69

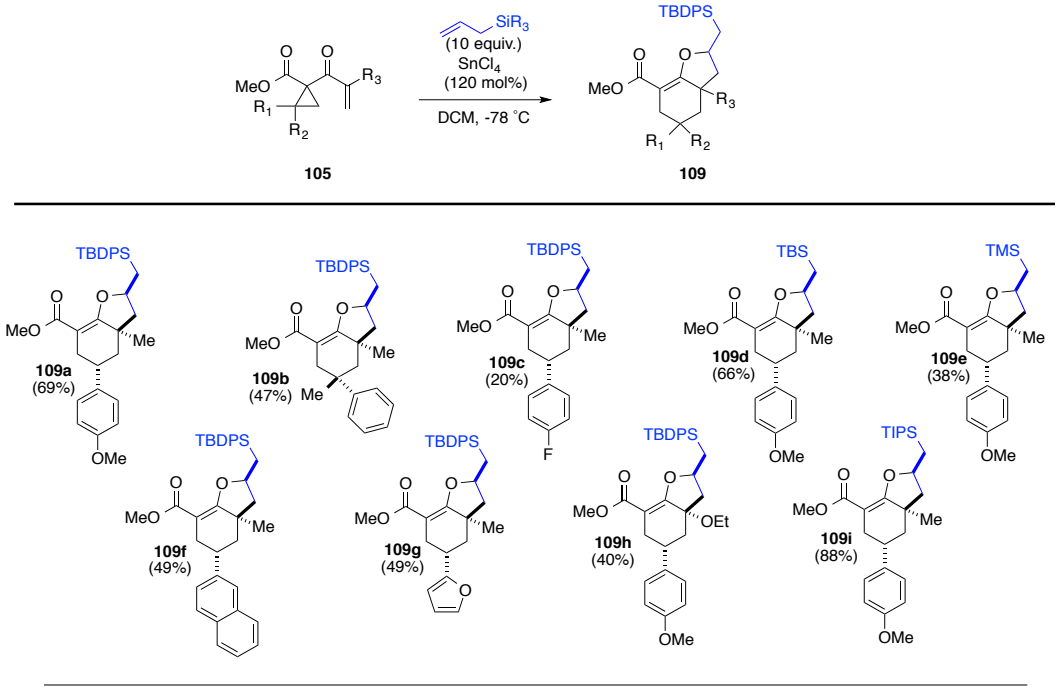
[a] Reaction run with 1 equiv of **108**, 10 equiv of allyl-TMS, and x mol% Lewis acid at room temp in DCM (y M). [b] Isolated yield after column chromatography. Attempts towards other Lewis acids were unsuccessful.

Scheme 2.19. An Alkyative Interrupted Homo-Nazarov Cycization.

2.6.1 Chemodivergence: Reaction Scope and Limitations

The unusual formal [3+2]-cycloaddition pathway for interrupting the homo-Nazarov reaction proved moderately robust and was extended to a variety of cyclopropanes and allylsilanes (Scheme 2.20). Correlations between cyclopropane donor groups and eventual yields of the trapped products follow trends similar to those observed in the allylative variant of the interrupted homo-Nazarov cyclization. In addition, sterically encumbered allylsilanes such allyl-TBDPS, allyl-TBS and allyl-TIPS afforded modest to high yields of hexahydrobenzofuran products **109** (up to 88% yield).

Less bulky silanes, such as allyl-TMS, were not well-tolerated and led to low yield of **109e** (38%).



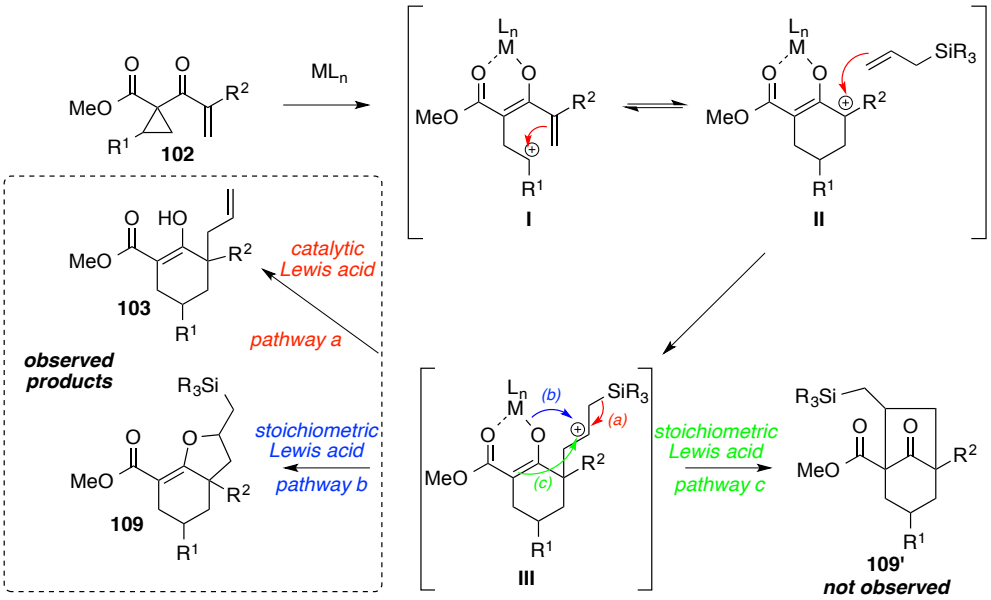
[a] Stereochemistry shown is for the major diastereomer.

Scheme 2.20. Scope of the Alkyative Interrupted Homo-Nazarov Cyclization.

2.6.2 Mechanistic Rationalization of Chemodivergent Reaction Outcomes

Our study utilized D-A-A cyclopropanes of the type **102** as substrates. Catalytic $SnCl_4$ in presence of allyl-TMS at room temperature led to allylated cyclohexenols **103** in good to high yields and complete regioselectivity (Scheme 2.21). On the other hand, stoichiometric $SnCl_4$ at lowered temperatures using bulkier allyl-TBDPS afforded hexahydrobenzofurans **109**. This chemodivergent trend can be fully rationalized by mechanistic considerations. β-silyl carbocations **III**, formed through nucleophilic trapping of oxyallyl cation **II**, are easily desilylated in the case of the labile TMS group leading to allylated products **103** (Hosomi-Sakurai reaction – pathway (c)). Conversely, the sterically encumbered groups, such as TBDPS, hinder desilylation and subsequent

enolate *O*-alkylation (formal [3+2]-cycloaddition – pathway (b)) leading to hexahydrobenzofuran formation. It should be noted that a third possibility, enolate *C*-alkylation, would have produced bicyclic ketones **109'** (pathway (c)). However, this product was not observed during this study presumably due to the reduced nucleophilicity at the α-carbon due to the electron-withdrawing ester group. The chemodivergent pathways for homo-Nazarov interruption provided entry into functionalized cyclohexenols **103** and hexahydrobenzofurans **104**. Moreover, the modularity and broad scope of this developed method proved particularly exciting.

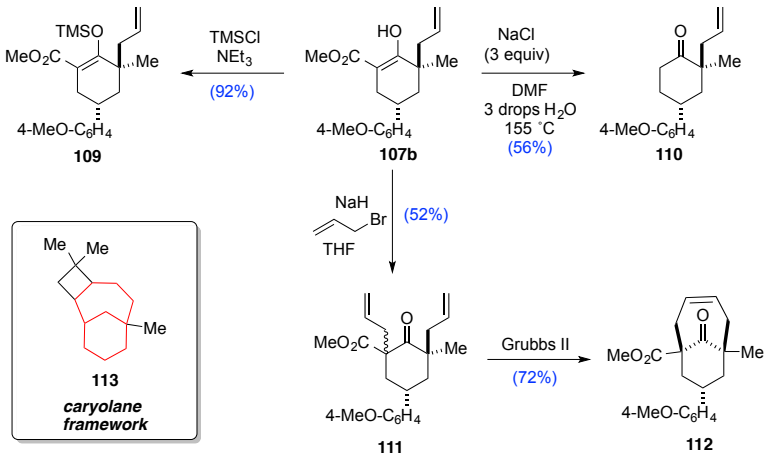


Scheme 2.21. Mechanism of Interrupted Homo-Nazarov Cyclizations.

2.7 Interrupted homo-Nazarov Products: Reaction Utility

The synthetic utility of our interrupted homo-Nazarov cyclization was demonstrated via chemical derivatizations of the obtained allyl-cyclohexenol compounds (Scheme 2.22). TMS-protection was carried out on cyclohexenol **107b** to provide enol-ether **109**, a candidate for further derivations. Krapcho decarbalkoxylation of **107b** led to ketone **110**. More interestingly, an allylation and ring-closing metathesis sequence to

yielded bicyclo[4.3.1.]dec-3-ene **112**, an important caryolane-type natural products framework (**113**).[27] This synthetic utility justifies interruption of the homo-Nazarov reaction as a useful tool for broader chemical applications.



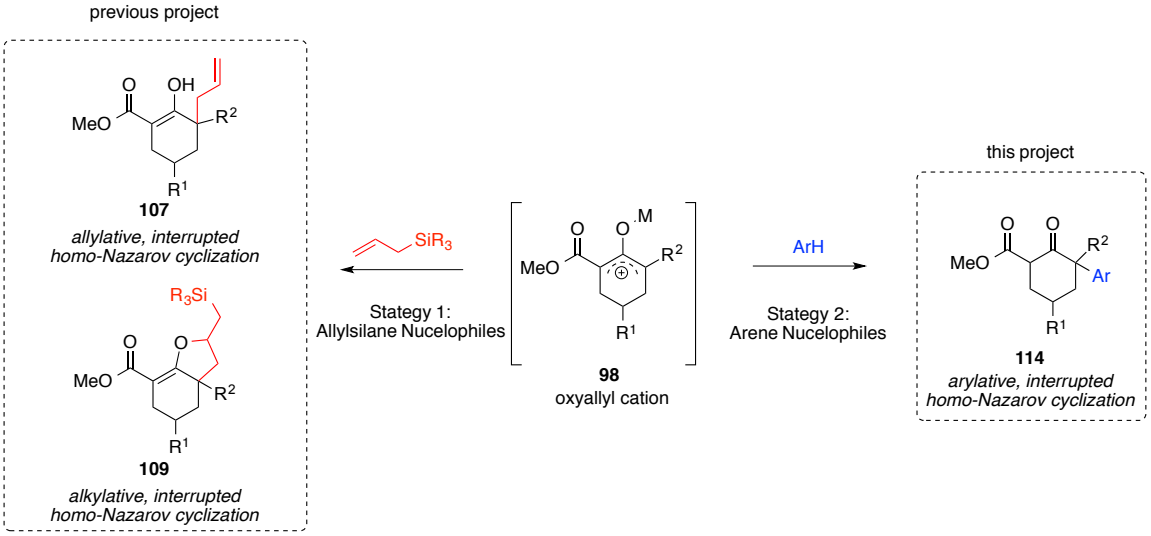
Scheme 2.22. Chemical Derivatizations of Interruption Products.

2.8 A (Hetero)arylative Interrupted Homo-Nazarov Cyclization

2.8.1 Reaction Design

Having established effective allylative and alkylative strategies (using allylsilane nucleophiles) for an interrupted homo-Nazarov reaction, we turned our attention to the previously unexplored (hetero)arylative variants (Scheme 2.23). We envisioned capturing the previously described oxyallyl cation intermediates with arenes and heteroarenes to afford interesting α-(hetero)aryl cyclohexanones. The nature of this cation capture by the (hetero)arene nucleophile would be an intermolecular Friedel-Crafts-type arylation of the intermediate oxyallyl cation **98**. Just as with our previously described allylsilane-interrupted homo-Nazarov chemistry, D-A-A cyclopropanes would be used as precursors for regiospecific (hetero)arylations. While unknown in the context of homo-Nazarov

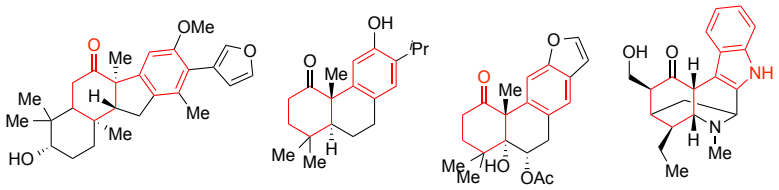
cyclizations, (hetero)arylative interrupted Nazarov reactions[10, 14b, 14g] have previously been explored and reported.



Scheme 2.23. Divergent Interrupted Homo-Nazarov Cyclizations.

2.8.2 Project Rationale and Justification

Successful implementation of aryl and heteroaryl nucleophiles for an interrupted homo-Nazarov cylization would allow entry into a variety of α-(hetero)aryl cyclohexanones, key structural motifs in numerous interesting and bioactive natural products (Figure 2.1). Examples of natural products bearing a α-(hetero)aryl cyclohexanone core include walsucochinoid D (**115**),[28] an effective human 11β-HSD1 inhibitor and the antibacterial agent diterpenoid 1-oxofurruginol (**116**).[29] Other structurally interesting α-(hetero)aryl cyclohexanone-type natural products have been identified and include the cassane-type diterpenoid caesall (**117**)[30] and indole alkaloid jadiffine (**118**).[31]



115 walsucochinoid D

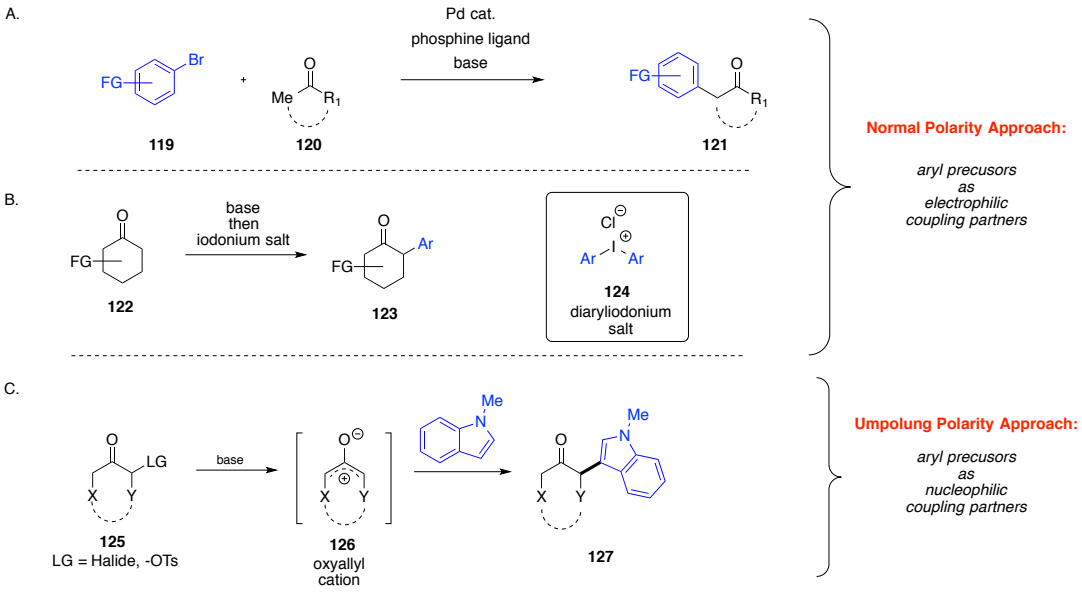
116 1-oxofurruginol

117 caesall I

118 jadiffine

Figure 2.1. α-Arylated Cyclohexenone Natural Products.

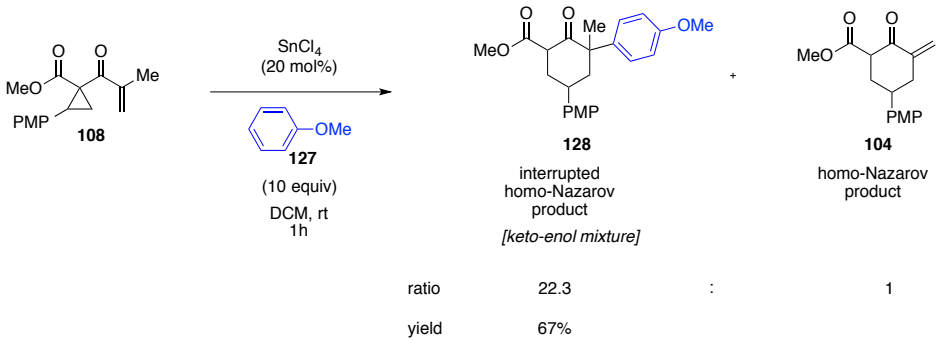
As a result of the structural diversity as well as the biological activity of α-(hetero)aryl cyclohexanone-type natural products, synthetic chemists have sought to establish versatile methods for synthesis of this core. Some of the most commonly used methods include transition metal-catalyzed direct α-arylation of ketones **120** using bromoarenes **119** as the aryl precursors (Scheme 2.24, A).[32] In addition, diarylidonium salts **124** have useful and environmentally-friendly synthetic precursors to α-(hetero)aryl ketones and aldehydes (Scheme 2.24, B).[33] Both these methods can often be performed in an asymmetric fashion and feature a normal polarity approach in which the aryl precursors act as the electrophilic coupling partners. In contrast, (hetero)aryl precursors can react as nucleophilic coupling partners (umpolung approach) as demonstrated by MacMillan's indole-capture of cyclic and acyclic oxyallyl intermediates (Scheme 2.24, C).[8] These oxyallyl cations were, in turn, generated from α-tosylketones **125** in a transformation reminiscent of the Favorskii reaction. As an extension of this umpolung chemistry, our planned arylative interrupted homo-Nazarov methodology would provide complementary entry into α-(hetero)aryl cyclohexanone scaffolds.



Scheme 2.24. α-Arylation Strategies in Literature.

2.8.3 Proof of Principle

To determine the potential for arenes as suitable nucleophiles for an interrupted homo-Nazarov cyclization, D-A-A cyclopropane **108** and anisole **127** were chosen as the model system (Scheme 2.25). Satisfactorily, oxyallyl cation-capture by anisole occurred smoothly, in a 22.3:1 selectivity, to afford α-arylated cyclohexanone **128** in 67% yield. Importantly, this example highlights the first instance of an arylative, interrupted homo-Nazarov reaction in literature.



Scheme 2.25. An Arylative Interrupted Homo-Nazarov Cyclization.

2.8.4 Reaction Optimization

Efforts were made to optimize the developed arylative transformation with several points of emphasis: (1) lowering the $SnCl_4$ loading or identifying a less toxic back-up catalyst; (2) increasing selectivity towards the desired, arylated product **128**; and (3) increasing chemical yield. An extensive Lewis acid screen using +4, +3, and +2 oxophilic Lewis acids revealed $SnCl_4$ to be the optimal Lewis acid at a 20 mol% loading (67% yield, 22:1 selectivity) (Table 2.5, entry 1). $InCl_3$, albeit slow, was a competent catalyst affording the desired aryl ketone **128** in 69% yield and 12:1 selectivity (Table 2.5, entry 8). All other Lewis acids screened, expect for $Mg(OTf)_2$, were disappointing, favoring either degradation pathways or exclusive formation of the undesired homo-Nazarov product **104** (Table 2.5).

Table 2.5. Lewis Acid Screen for Arylative Interruption[a].

entry	Lewis acid	time (h)	yield of **128**[b] (%)	**128** : **104**[c]
1	$SnCl_4$	1	67	22 : 1
2	$TiCl_4$	24	--	--[d]
3	$In(OTf)_3$	1	11	1 : 1.7
4	$Sc(OTf)_3$	1	10	1 : 1.5
5	$Al(OTf)_3$	1	--	--[d]
6	$Ga(OTf)_3$	1	--	--[d]
7	$Yb(OTf)_3$	1	--	--[d]
8	$InCl_3$	24	69	12 : 1
9	$BF_3 \bullet OEt_2$	1	--	--[d]
10	$Ca(NTf)_2 \bullet nBu_4NPF_6$	0.5	--	--[d]
11	$Zn(OTf)_2$	1.5	--	--[d]
12	$Cu(OTf)_2$	1.5	--	--[d]
13	$Mg(OTf)_2$	48	63	6 : 1[e]

[a] Reaction run with 1 equiv of **108**, 10 equiv of anisole **127**, and 20 mol% Lewis acid at room temp in DCM (0.1 M). [b] Isolated yield after column chromatography. [c] Ratio determined by ^{1}H-NMR. [d] No desired product oberved. [e] Product had impurities.

The two best catalysts, $SnCl_4$ and $In(OTf)_3$, were subjected to further optimization (Table 2.6). Lowering the loading of $SnCl_4$ did not lead to any improvement in yield. On the other hand attempts to lower the catalyst loading of $In(OTf)_3$ were more fruitful – a loading of 10 mol% produced the desired product in 62% (Table 2.6, entry 6) virtually similar to the results at a loading of 20 mol% (Table 2.6, entry 4). Attempts to change other variables such as concentration, temperature, solvent and loading of anisole did not lead to any significant reaction enhancement. Therefore 20 mol% $SnCl_4$ (Table 2.6, entry 1) was moved forward as the optimal Lewis acid, with $In(OTf)_3$ (10 mol%) (Table 2.6, entry 6) serving as a suitable, non-toxic backup catalyst.

Table 2.6. Lewis Acid Optimization[a].

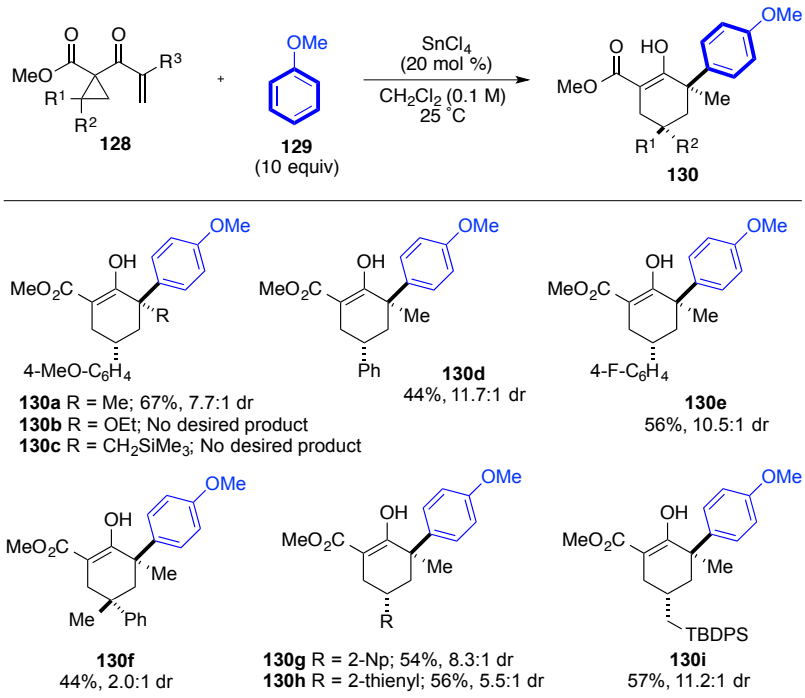
entry	Lewis acid	Loading (mol%)	time (h)	yield of **128**[b] (%)
1	$SnCl_4$	20	1	67
2	$SnCl_4$	10	1	56
3	$SnCl_4$	5	1	50
4	$InCl_3$	20	24	69
5	$InCl_3$	15	24	65
6	$InCl_3$	10	24	62
7	$InCl_3$	5	24	38

[a] Reaction run with 1 equiv of **108**, 10 equiv of anisole, and x mol% Lewis acid at room temp in DCM (0.1 M). [b] Isolated yield after column chromatography.

2.8.5 Reaction Scope and Limitations

Upon optimization of reaction conditions, a systematic investigation of the scope and limitations of the arylative variant to the interrupted homo-Nazarov cyclization was commenced. First, the tolerance of this transformation for differently substituted cyclopropanes was probed using anisole as the nucleophilic trapping agent (Scheme 2.26). A methyl-substituted enone unit was tolerated and smoothly afforded arylated

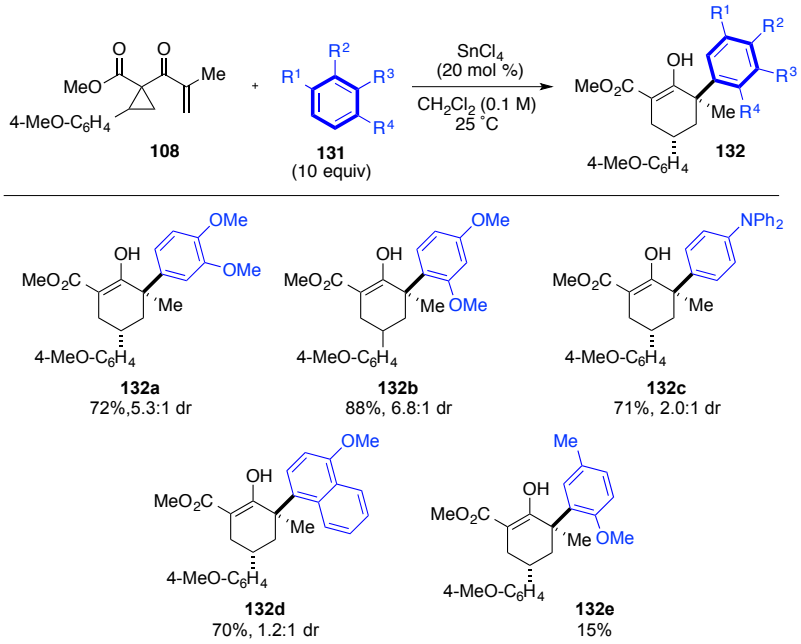
product **130a** in 67% yield while methylenesilyl and ethoxy substituents did not afford any desired products (**130a** and **130c**) presumably due to the reduced electrophilicity of the oxyallyl cation intermediate. On the other hand, the use of different donor groups on the cyclopropane did not have a significant impact on reaction yield; arylated products **130d**-**130i** were obtained in modest 44-57% yields.



Scheme 2.26. Scope of Arylative Interruption Using Different D-A-A Cyclopropanes.

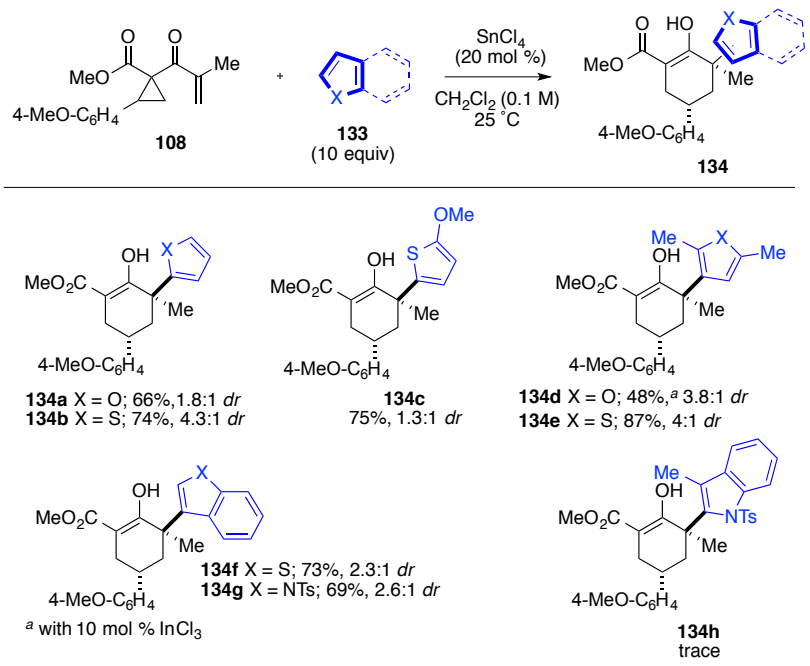
Next, benzene derivatives other than anisole were investigated as trapping agent using D-A-A cyclopropane **108** (Scheme 2.27). As expected for Friedel-Crafts-type processes, more electron-rich derivatives performed better relative to anisole as trapping agents. 1,2- and 1,3-dimethoxybenze smoothly afforded products **132a** and **132b** in 72% and 88% yields respectively. Triphenylamine and 1-methoxynaphthalene were also well-tolerated and furnished their respective products **132c** and **132d** in 71% and 70% yields. Blocking the 4-position of anisole with a methyl groups (use of 4-methlanisole) forced

ortho-substitution (**132e**), albeit in a lowered yield. This pointed towards a steric sensitivity of these arylative interrupted homo-Nazarov cyclizations. In addition, less activated benzenes such as toluene, halobenzenes, and TMS-benzene proved to be weak nucleophiles and did not afford any desired products at all.



Scheme 2.27. Scope of Arylative Interruption with Benzene Derivatives.

Finally, our focus shifted to heteroaromatics as nucleophiles for capturing the intermediate oxyallyl cation (Scheme 2.28). These heteroaromatics proved to be competent nucleophiles indeed. Thiophene, furan, and derivatives thereof afforded α-(hetero)arylated cyclohexenols **134a**-**134e** in good to high yields (48%-87%). Benzo-fused heteroaromatics, such as benzofuran and *N*-tosylindole, readily underwent 3-alkylations to affords products **134f** and **134g** in 73% and 69% yields respectively. Interestingly, *N*-tosyl-3-methylindole failed to afford significant amounts of desired product (**134h**), presumably due to steric hindrance of the methyl group as well as the reduced nucleophilicity of the C-2 position.



Scheme 2.28. Scope of Arylative Interruption with Heteroarenes.

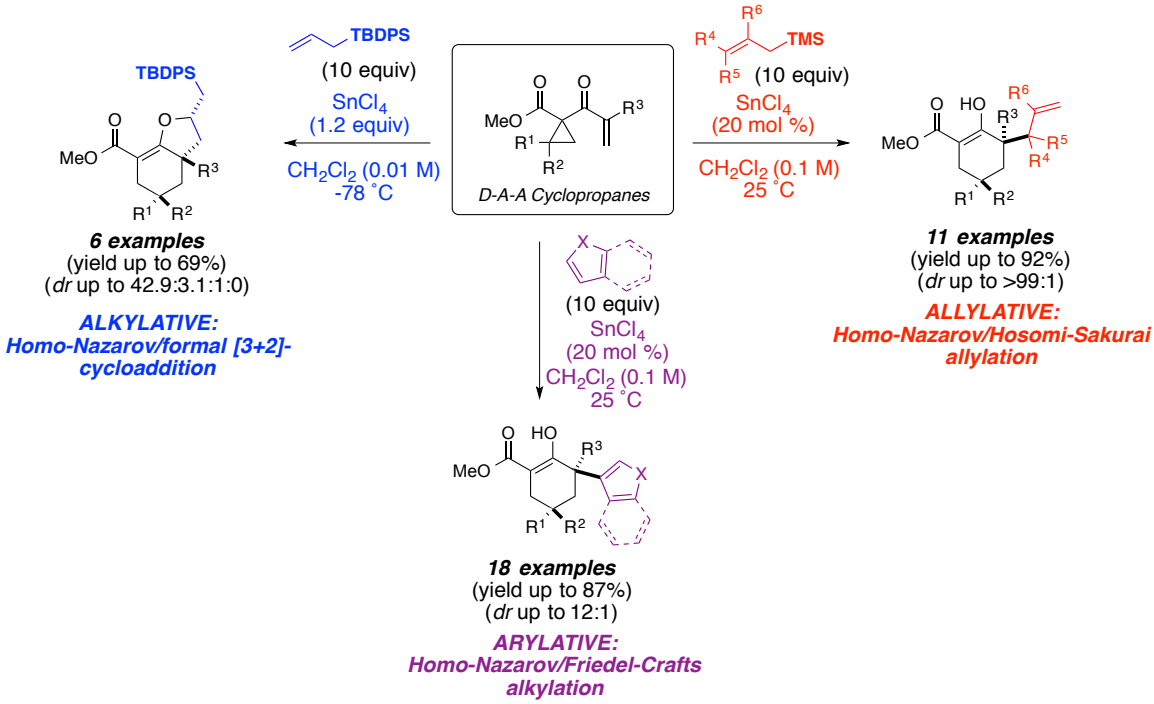
Although all products were obtained as intractable diastereomeric keto-enol mixtures, subsequent Krapcho decarbalkoxylations enabled definitive NMR analysis that revealed a *trans* relationship between the aryl substituents. On approaching the oxyallyl cation intermediate, an incoming arene nucleophile presumably attacks from the side opposite the donor group so as to minimize unfavorable 1,3-diaxial interactions leading to the observed stereochemistry.

2.9 Summary: Allylative, Alkylative and Arylative Interrupted Homo-Nazarov Cyclizations

While the homo-Nazarov cyclization has increasingly become a notable strategy for the assembly of medium-sized polycyclic scaffolds, its interrupted variant remains relatively underexplored. Presented in this chapter are the first literature reports of interrupted homo-Nazarov cyclizations in which nucleophilic trapping agents capture the intermediate oxyallyl cation. This oxyallyl cation intermediate originates from

intramolecular ring-opening/cyclization of D-A-A cyclopropanes under mild Lewis acid conditions.

Using catalytic amounts of $SnCl_4$ and in the presence of allylsilane nucleophiles, tandem homo-Nazarov cyclization/Hosomi-Sakurai reactions afford allylated cyclohexenols good to high yields as well as reasonable diastereoselectivity (Scheme 2.29). In contrast, a chemodivergent, alkylative variant is possible using stoichiometric $SnCl_4$ at lowered temperatures in the presence of bulky allylsilanes. In this case a homo-Nazarov cyclization/formal [3+2]-cycloaddition pathway leads to the formation of hexahydrobenzofurans. Additionally, a follow-up study revealed that allylsilanes are not the only nucleophiles tolerated in interrupted homo-Nazarov cyclizations. Use of activated arenes and heteroarenes in a tandem homo-Nazarov/Friedel-Craft alkylation fashion enable synthesis of α-(hetero)arylated cyclohexanones under catalytic $SnCl_4$ conditions. These generalized protocols serve as the benchmark transformations for allylative, alkylative and arylative interrupted homo-Nazarov cyclizations in literature.



Scheme 2.29. Chemodivergent Interruption of the Homo-Nazarov Cyclization.

2.10 EXPERIMENTAL SECTION

- For supporting information (including experimental section and characterization) for interrupted homo-Nazarov reactions using allylsilanes see: Shenje, R.; Williams, C. W.; Francois, K. M.; France, S., Catalysis and Chemodivergence in the Interrupted, Formal Homo-Nazarov Cyclization Using Allylsilanes. *Org. Lett.* **2014,** *16* (24), 6468-6471.
- For supporting information (including experimental section and characterization) for interrupted homo-Nazarov reactions using (hetero)aromatics see: Shenje, R.; Williams, C. W.; France, S., Catalytic, Interrupted Formal Homo-Nazarov Cyclization with (Hetero)arenes: Access to α-(Hetero)aryl Cyclohexanones. *Manuscript in Revision*.

2.11 REFERENCES

1. Shenje, R.; Williams, C. W.; Francois, K. M.; France, S., Catalysis and Chemodivergence in the Interrupted, Formal Homo-Nazarov Cyclization Using Allylsilanes. *Org. Lett.* **2014,** *16* (24), 6468-6471.

2. Hoffmann, H. M. R., Syntheses of Seven- and Five-Membered Rings from Allyl Cations. *Angew. Chem. Int. Ed.* **1973,** *12* (10), 819-835.

3. Hill, A. E.; Greenwood, G.; Hoffmann, H. M. R., Cycloadditions and reactivity of 2-methoxyallyl halides. *J. Am. Chem. Soc.* **1973,** *95* (4), 1338-1340.

4. Hoffmann, H. M. R., The Cycloaddition of Allyl Cations to 1,3-Dienes: General Method for the Synthesis of Seven-Membered Carbocycles. New Synthetic Methods (40). *A Angew. Chem. Int. Ed.* **1984,** *23* (1), 1-19.

5. Mann, J., The synthetic utility of oxyallyl cations. *Tetrahedron* **1986,** *42* (17), 4611-4659.

6. (a) Li, H.; Wu, J., (3+ 2)-Cycloaddition Reactions of Oxyallyl Cations. *Synthesis* **2015,** *47* (1), 22; (b) Li, H.; Hughes, R. P.; Wu, J., Dearomative Indole (3 + 2) Cycloaddition Reactions. *J. Am. Chem. Soc.* **2014,** *136* (17), 6288-6296.

7. Lohse, A. G.; Hsung, R. P., (4+3) Cycloaddition Reactions of Nitrogen-Stabilized Oxyallyl Cations. *Chem. Eur. J.* **2011,** *17* (14), 3812-3822.

8. Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C., Development of a generic activation mode: nucleophilic [small alpha]-substitution of ketones via oxy-allyl cations. *Chem. Sci.* **2013,** *4* (8), 3075-3079.

9. Harmota, M., The Nazarov reaction: substituent effects, catalysis and asymmetric catalysis. *Chemtracts,* **2004,** ***17,*** 416–435.10; Nakanishi, W.; West, F. G., Advances in the Nazarov cyclization. *Curr. Opin. Drug Discov. Devel.* **2009,** *12* (6), 732-751.

11. Liang, G.; Trauner, D., Enantioselective Nazarov Reactions through Catalytic Asymmetric Proton Transfer. *J. Am. Chem. Soc.* **2004,** *126* (31), 9544-9545.

12. Ma, Z.-X.; He, S.; Song, W.; Hsung, R. P., α-Aryl-Substituted Allenamides in an Imino-Nazarov Cyclization Cascade Catalyzed by Au(I). *Org. Lett.* **2012,** *14* (22), 5736-5739.

13. Rieder, C. J.; Winberg, K. J.; West, F. G., Cyclization of Cross-Conjugated Trienes: The Vinylogous Nazarov Reaction. *J. Am. Chem. Soc.* **2009,** *131* (22), 7504-7505.

14. (a) Berger, G. O.; Tius, M. A., Total Synthesis of (±)-Terpestacin and (±)-11-epi-Terpestacin. *J. Org. Chem.* **2007,** *72* (17), 6473-6480; (b) Frontier, A. J.; Collison, C., The Nazarov cyclization in organic synthesis. Recent advances. *Tetrahedron* **2005,** *61* (32), 7577-7606; (c) He, W.; Huang, J.; Sun, X.; Frontier, A. J., Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization. *J. Am. Chem. Soc.* **2007,** *129* (3), 498-499; (d) He, W.; Huang, J.; Sun, X.; Frontier, A. J., Total Synthesis of (±)-Merrilactone A. *J. Am. Chem. Soc.* **2008,** *130* (1), 300-308; (e) Malona, J. A.; Cariou, K.; Frontier, A. J., Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009,** *131* (22), 7560-7561; (f) Malona, J. A.; Cariou, K.; Spencer, W. T.; Frontier, A. J., Total Synthesis of (±)-Rocaglamide via Oxidation-Initiated Nazarov Cyclization. *J. Org. Chem.* **2012,** *77* (4), 1891-1908; (g) Tius, M. A., Some New Nazarov Chemistry. *Eur. J. Org. Chem.* **2005,** *2005* (11), 2193-2206; (h) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P., Strategies for the Synthesis of Fusicoccanes by Nazarov Reactions of Dolabelladienones: Total Synthesis of (+)-Fusicoauritone. *Angew. Chem. Int. Ed.* **2007,** *46* (6), 915-918.

15. (a) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J., Formal Homo-Nazarov and Other Cyclization Reactions of Activated Cyclopropanes. *Chem. Eur. J.* **2011,** *17* (51), 14527-14538; (b) Di Grandi, M. J., Nazarov-like cyclization reactions. *Org. Biomol. Chem.* **2014,** *12* (29), 5331-5345; (c) De Simone, F.; Waser, J., Cyclization of Cyclopropyl Carbonyls and the Homo-Nazarov Reaction. *CHIMIA* **2009,** *63* (3), 162-167.

16. (a) Murphy, W. S.; Wattanasin, S., A new cyclisation involving cyclopropyl ketones. A short route to 1-aryltetralones. *Tetrahedron Lett.* **1980,** *21* (19), 1887-1890; (b) Yadav, V. K.; Kumar, N. V., 2,3-Heteroaromatic ring-fused cyclohexanonesvia heteroaromatic homo-Nazarov cyclization of donor-acceptor substituted cyclopropanes. *Chem. Commun.* **2008,** (32), 3774-3776.

17. Hanson, J. R., The viridin family of steroidal antibiotics. *Nat. Prod. Rep.* **1995,** *12* (4), 381-384.

18. Dewick, P. M., *Medicinal natural products: a biosynthetic approach*. John Wiley & Sons: **2002**.

19. Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M., Total synthesis of (+)-actinobolin. *J. Am. Chem. Soc.* **1985,** *107* (25), 7790-7792.

20. Mizuki, K.; Iwahashi, K.; Murata, N.; Ikeda, M.; Nakai, Y.; Yoneyama, H.; Harusawa, S.; Usami, Y., Synthesis of Marine Natural Product (−)-Pericosine E. *Org. Lett.* **2014,** *16* (14), 3760-3763.

21. Martin, M. C.; Shenje, R.; France, S., The Catalytic, Formal Homo-Nazarov Cyclization as a Template for Diversity-Oriented Synthesis. *Isr. J. Chem.* **2016**, n/a-n/a.

22. Patil, D. V.; Phun, L. H.; France, S., Indium-Catalyzed Homo-Nazarov Cyclizations of Alkenyl Cyclopropyl Ketones. *Org. Lett.* **2010,** *12* (24), 5684-5687.

23. Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S., A Catalytic Homo-Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones. *Org. Lett.* **2011,** *13* (8), 1952-1955.

24. (a) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S., An efficient synthesis of hydropyrido[1,2-a]indole-6(7H)-ones via an In(iii)-catalyzed tandem cyclopropane ring-opening/Friedel-Crafts alkylation sequence. *Chem. Commun.* **2011,** *47* (37), 10278-10280; (b) Aponte-Guzmán, J.; Taylor, J. E.; Tillman, E.; France, S., Catalytic, Formal Homo-Nazarov-Type Cyclizations of Alkylidene Cyclopropane-1,1-Ketoesters: Access to Functionalized Arenes and Heteroaromatics. *Org. Lett.* **2014,** *16* (14), 3788-3791; (c)

Cavitt, M. A.; Phun, L. H.; France, S., Intramolecular donor-acceptor cyclopropane ring-opening cyclizations. *Chem. Soc. Rev.* **2014,** *43* (3), 804-818; (d) Patil, D. V.; Cavitt, M. A.; France, S., Diastereoselective Synthesis of (±)-Deethyleburnamonine Using A Catalytic Cyclopropane Ring-Opening/Friedel-Crafts Alyation Strategy (Dedicated to Dr. Albert Padwa on his 75th birthday). *Heterocycles* **2012,** *84* (2), 1363-1373; (e) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J., Catalytic Formal Homo-Nazarov Cyclization. *Org. Lett.* **2009,** *11* (4), 1023-1026.

25. (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G., Highly Diastereoselective Cycloisomerization of Acyclic Trienones. The Interrupted Nazarov Reaction. *J. Org. Chem.* **1998,** *63* (8), 2430-2431; (b) Grant, T. N.; Rieder, C. J.; West, F. G., Interrupting the Nazarov reaction: domino and cascade processes utilizing cyclopentenyl cations. *Chem. Commun.* **2009,** (38), 5676-5688; (c) Basak, A. K.; Tius, M. A., Interrupting the Nazarov Cyclization with Indoles. *Org. Lett.* **2008,** *10* (18), 4073-4076.

26. Yadav, V. K.; Naganaboina, V. K.; Hulikal, V., Allylsilane-interrupted homo-Nazarov cyclization and synthesis of bicyclo[3.2.1]octan-8-ones. *Tetrahedron Lett.* **2014,** *55* (12), 2015-2018.

27. (a) Goldring, W. P. D.; Paden, W. T., A ring-closing metathesis approach to the bicyclo[4.3.1]decane core of caryolanes. *Tetrahedron Lett.* **2011,** *52* (8), 859-862; (b) He, X.-F.; He, Z.-W.; Jin, X.-J.; Pang, X.-Y.; Gao, J.-G.; Yao, X.-J.; Zhu, Y., Caryolane-type sesquiterpenes from Cirsium souliei. *Phytochem. Lett.* **2014,** *10*, 80-85; (c) Huang, H.; Gao, X. J.; Liu, J.; Li, S.; Han, Y. F.; Zhou, B. C.; Xia, M., A new caryolane sesquiterpene from Heteropappus altaicus (Willd.) Novopokr. *Nat. Prod. Res.* **2013,** *27* (4-5), 350-355.

28. Han, M.-L.; Shen, Y.; Leng, Y.; Zhang, H.; Yue, J.-M., New rearranged limonoids from Walsura cochinchinensis. *RSC Adv.* **2014,** *4* (37), 19150-19158.

29. Topçu, G.; Gören, A. C., Biological activity of diterpenoids isolated from Anatolian Lamiaceae plants. *Rec. Nat. Prod* **2007,** *1* (1), 1-16.

30. Wu, L.; Wang, X.; Shan, S.; Luo, J.; Kong, L., New Cassane-Type Diterpenoids from Caesalpinia bonduc. *Chem. Pharm. Bull.* **2014,** *62* (7), 729-733.

31. Garnier, J.; Mahuteau, J.; Plat, M.; Merienne, C., The complete assignment of the ^{13}C and ^{1}H NMR spectra of jadiffine. *Phytochemistry* **1989,** *28* (1), 308-309.

32. Potukuchi, H. K.; Spork, A. P.; Donohoe, T. J., Palladium-catalyzed α-arylation of carbonyls in the de novo synthesis of aromatic heterocycles. *Org. Biomol. Chem.* **2015,** *13* (15), 4367-4373.

33. Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C., Hypervalent iodine: a powerful electrophile for asymmetric [small alpha]-functionalization of carbonyl compounds. *Org. Biomol. Chem.* **2014,** *12* (25), 4278-4289.

34. González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M., Rhodium-Catalyzed Cyclopropanation of Alkenes with Dimethyl Diazomalonate. *Adv. Synth. Catal.* **2008,** *350* (6), 813-816.

35. Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y., Nickel-Catalyzed Addition of Dimethylzinc to Aldehydes across Alkynes and 1,3-Butadiene: An Efficient Four-Component Connection Reaction. *J. Am. Chem. Soc.* **2005,** *127* (1), 201-209.

CHAPTER 3 FORMAL [5+2]-CYCLOADDITIONS VIA DONOR-ACCEPTOR CYCLOBUTANES: SYNTHESIS OF AZEPINO[1,2-*A*]INDOLES AND CYCLOHEPTA[*B*]INDOLES[§,**,1]

3.1 Azepino[1,2-*a*]indoles and Cyclohepta[*b*]indoles In Natural Products

Indole-based alkaloids are ubiquitous in nature; there are well over 12000 identified natural products containing this moiety.[2] While this family of compounds demonstrates an astonishing degree of structural diversity, it also possesses an equally impressive range of biological activities. Many indole alkaloids are known to have anticancer, antimalarial, and anti-arrhythmic activities among many other bioactivities.[2b, 3] Famous examples of well-studied indole alkaloids include lysergic acid,[4] vinblastine,[5] tabersonine,[6] and strychnine[7] among others. Despite their chemical diversity, many indole alkaloids share the same biogenetic precursor – tryptophan, which undergoes divergent biosynthetic routes to afford the observed rich chemical diversity.[8] This combination of intriguing structural complexity and biological activity has made indole alkaloids some of the most extensively studied natural products by chemists. As a

---

[§] Work on synthesis of azepino[1,2-a]indoles performed in collaboration with M. Cynthia Martin. Published in *Angew. Chem. Int. Ed*. **2014**, 53, 13907.

[**] Work on synthesis of cyclohepta[*b*]indoles performed in collaboration with M. Cynthia Martin. Manuscript in preparation.

consequence, numerous methodologies have been developed, and many total syntheses attempted, to allow entry into this family in a concise and stereoselective fashion.[9]

Among the indole alkaloid family of natural products are two interesting subclasses – the azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles (Figure 3.1). Azepino[1,2-*a*]indole **1**, correantine B,[10] exemplifies a set of exciting compounds from *Psychotria correae* while the structurally similar akagerine (**2**)[11] possesses antiprotozoal activity. Azepines **3** and **4** possess activity in the prostaglandin D2 receptor[12] and cyclin-dependent kinase[13] realms, respectively, while **5** represents a vast library of small molecule compounds active against hepatitis C NS5B.[14] Along the same lines, compounds **6-9** depict diverse sets of natural products with interesting structure profiles or bioactivity in the cyclohepta[*b*]indole subfamily.[15] Many other azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles have demonstrated significant activity in a range of therapeutic areas.[16]

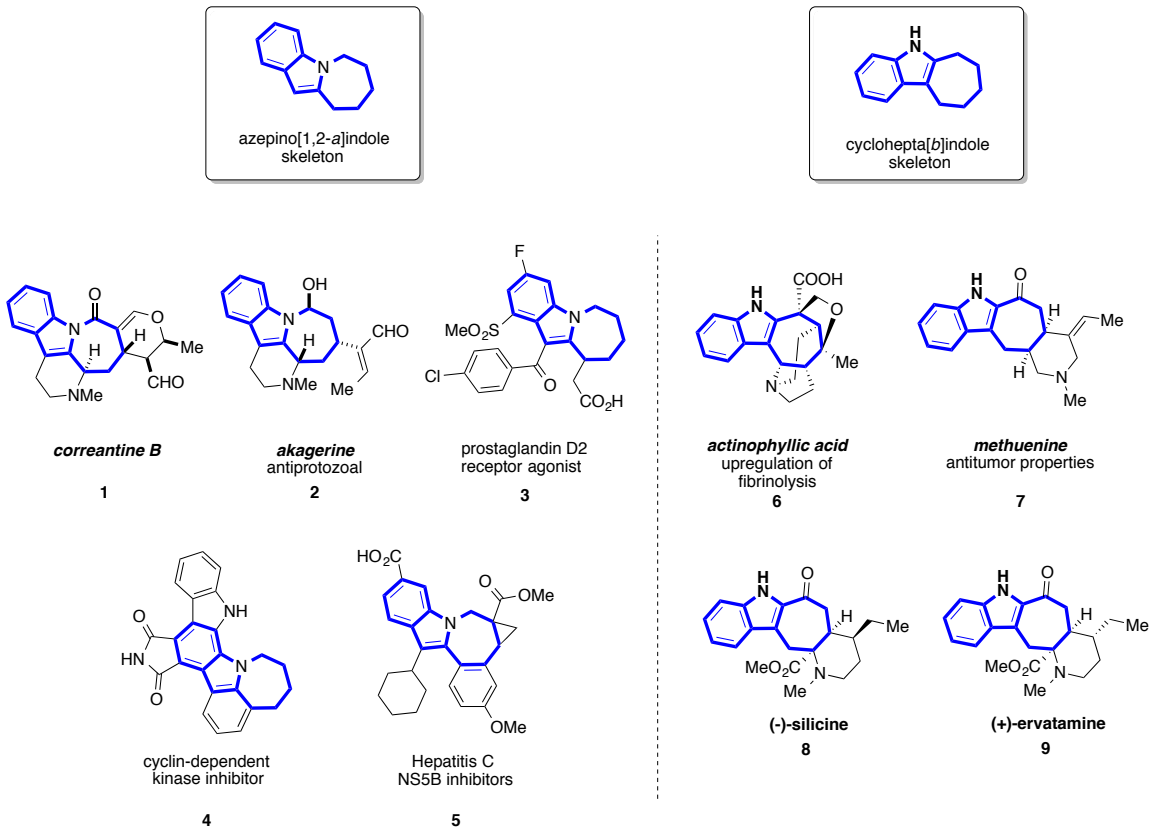
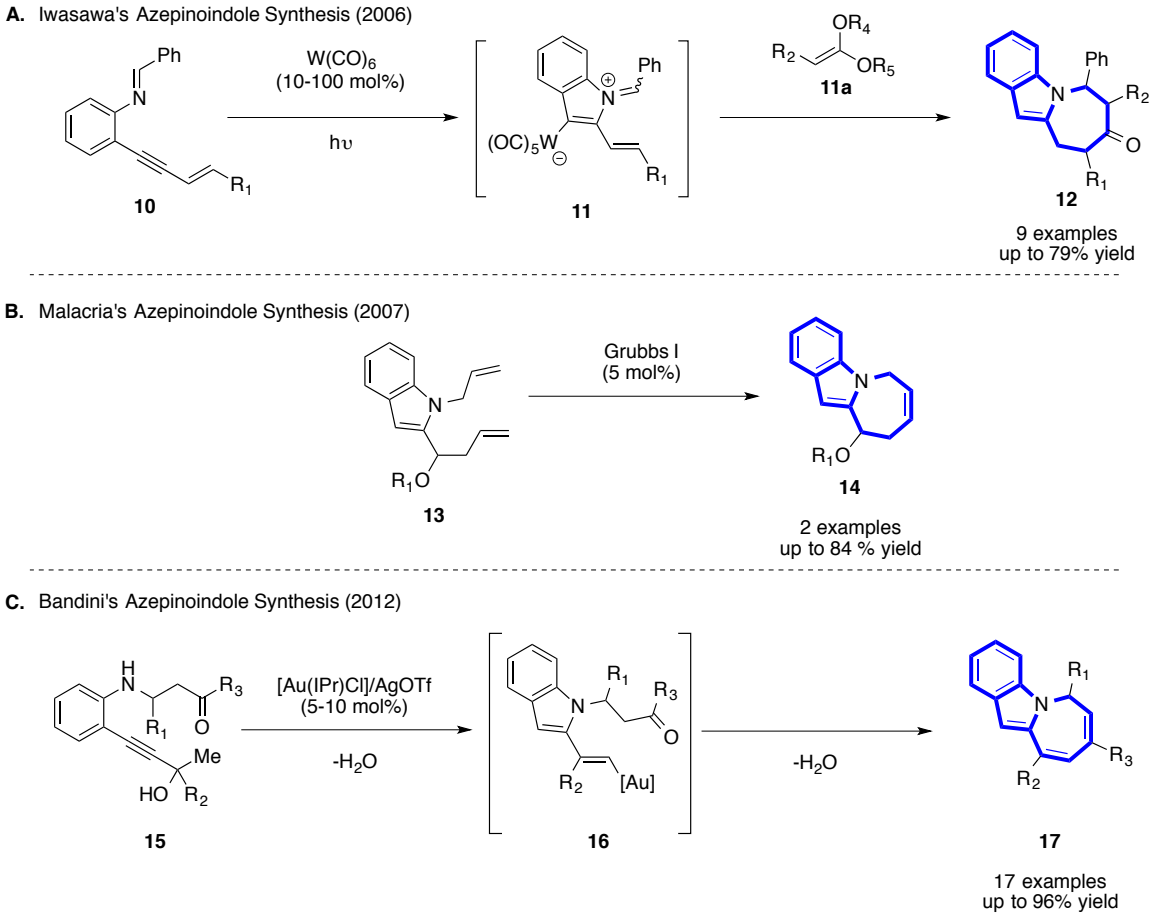


Figure 3.1. Azepino[1,2-*a*]indoles and Cyclohepta[*b*]indoles in Bioactive Natural Products.

Given their structural diversity, molecular complexity and intriguing biological activity, azepino[1,2-*a*]indole and cyclohepta[*b*]indole natural products (and cores thereof) have been subject to many synthetic endeavors.[1, 17] Both these two subclasses feature contiguous 6-5-7 ring fusions, scaffolds that have garnered considerable interest. Typical approaches to azepinoindoles have included: (1) hetero-[5+2] cycloadditions; (2) ring-closing olefin metatheses; (3) Lewis acid catalyzed intramolecular cyclizations; and (4) radical cyclizations (Scheme 3.1). As an example, a W-mediated cyclization of imino alkyne **10** was demonstrated, by Iwasawa and co-workers, to afford azomethine ylides **11** (Scheme 3.1, A).[17f] Subsequent hetero-[5+2] cycloadditions of these ylides with ketene acetals **11a** led to the formation of desired azepino[1,2-*a*]indoles **12**. In addition,

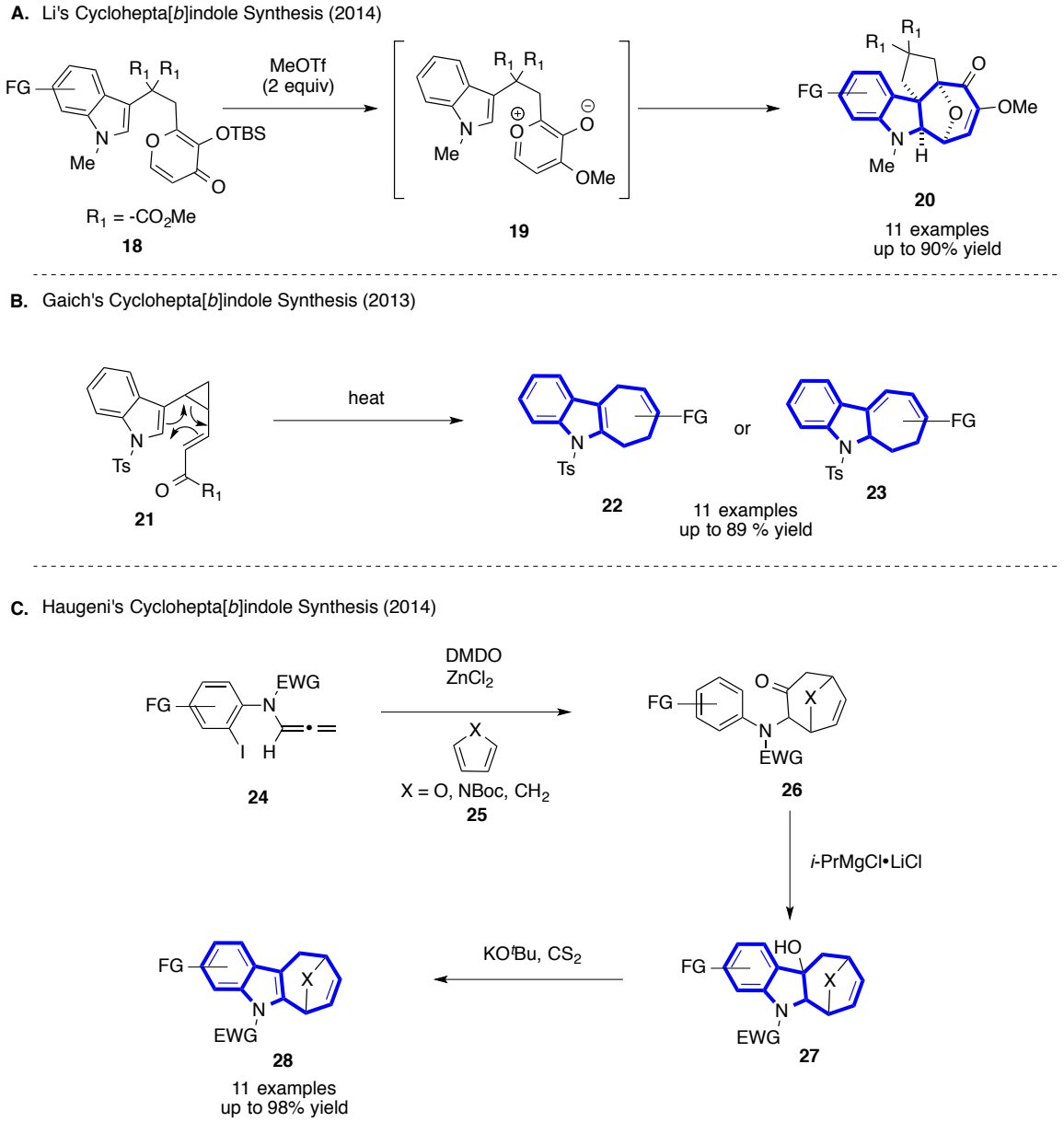
Malacria *et al*. devised a simple ring-closing metathesis approach to azepinoindoles **14** using indole-based dienes **13** (Scheme 3.1, B).[17b] More recently, Bandini and co-workers developed an effective synthesis to the azepinoindole core using a strategy that utilizes Au-catalyzed tandem hydroamination/dehydrative cyclizations to afford azepines **17** in good chemoselectivities and yields (up to 96%). (Scheme 3.1, C).[17c] While providing pioneering routes to the azepino[1,2-*a*]indole core, these strategies suffer from at least one of the following drawbacks: (1) high catalyst loadings; (2) low functional group tolerances; (3) limitations in substrate scope; and (4) utilization of cumbersome starting materials. With these limitations in mind, the France lab sought to develop a novel protocol for azepino[1,2-*a*]indole and cyclohepta[*b*]indole syntheses with particular emphasis on efficiency, selectivity, modularity and breadth of scope.



Scheme 3.1. Prior Synthetic Approaches to Azepino[1,2-*a*]indoles.

On the other hand, typical approaches to the cyclohepta[*b*]indole are shown in Scheme 3.2. Li *et al.* developed a powerful intramolecular [5+2]-cycloaddition of tethered indole **18** to form synthetically-challenging, densely-functionalized cyclohepta[*b*]indoles **20** (Scheme 3.2, A).[17g] This reaction proceeds via an intermediate oxidopyrylium ylide **19** that undergoes a dearomative cycloaddition *en route* to polycylic products **20**. Another method for cyclohepta[*b*]indole formation is through divinyl cyclopropyl rearrangement of indoles **21** to afford products **22** and **23** in good yields (Scheme 3.2, B).[17d] Mechanistically, this reaction occurs via a thermal [3,3]-sigmatropic rearrangement; the use of enantiopure cyclopropanes leads to consequent chirality

transfer to the cyclohepta[*b*]indole products. Finally, a notable three-step sequence for cyclohepta[*b*]indole synthesis was established by Haugen and co-workers from precursor allenamides **24** (Scheme 3.2, C).[17e] In an initial step, allenamides **24** undergo a DMDO-mediated epoxidation followed by $ZnCl_2$-promoted [4+3]-cycloaddition to afford bicyclic ketones **26**. Secondly, magnesium-halogen exchange generates a Grignard reagent that undergoes an intramolecular nucleophilic attack onto ketone **26** to afford alcohol **27**. Finally, a Chugaev elimination furnished highly functionalized cyclohepta[*b*]indoles **28**. While these ingenious protocols afforded highly useful cyclohepta[*b*]indoles, development of more concise methods for accessing the same molecular scaffold in a streamlined, modular fashion would be of immense benefit to the synthetic community.



Scheme 3.2. Prior Synthetic Approaches to Cyclohepta[*b*]indoles.

3.2 Development of a Formal [5+2] Approach to Azepino[1,2-a]indoles via Putative D-A-A Cyclobutanes Intermediates

3.2.1 Project Rationale and Justification

Our lab has consistently been fascinated by small, strained carbocycles as building blocks for molecular complexity and diversity. Much of our emphasis has been

on a specific class of cyclopropanes referred to as the donor-acceptor-acceptor (D-A-A) cyclopropanes. Chapter 1 described, in detail, the range of reactivities possible as well the scope of chemical scaffolds accessible using D-A-A cyclopropane building blocks. Over the past several years, the France lab has reported exciting protocols involving ring-opening cyclizations of these cyclopropanes for the synthesis of cyclohexenones (**28**), dihydrobenzofurans (**29**), cyclohexa[*b*]indoles (**30**), benzo[*c*]thiophenes (**31**), pyrido[1,2-*a*]indoles (**32**), and hydropyrido[1,2-*a*]indoles (**33**), and many other benzo-fused heteroaromatics (Figure 3.2, A).[18] In addition, our lab has showcased the utility of D-A-A cyclopropanes by applying them in the total synthesis of (±)-deethyleburnamonine (**34**) (Figure 3.2, A). Given this success with D-A-A cyclopropanes, we envisaged homologous intramolecular ring-opening reactivity using D-A-A cyclobutanes. Successful implementation of such a strategy would allow concise entry into azepino[1,2-*a*]indoles, an important scaffold in the indole alkaloid family of natural products (Figure 3.2, B).

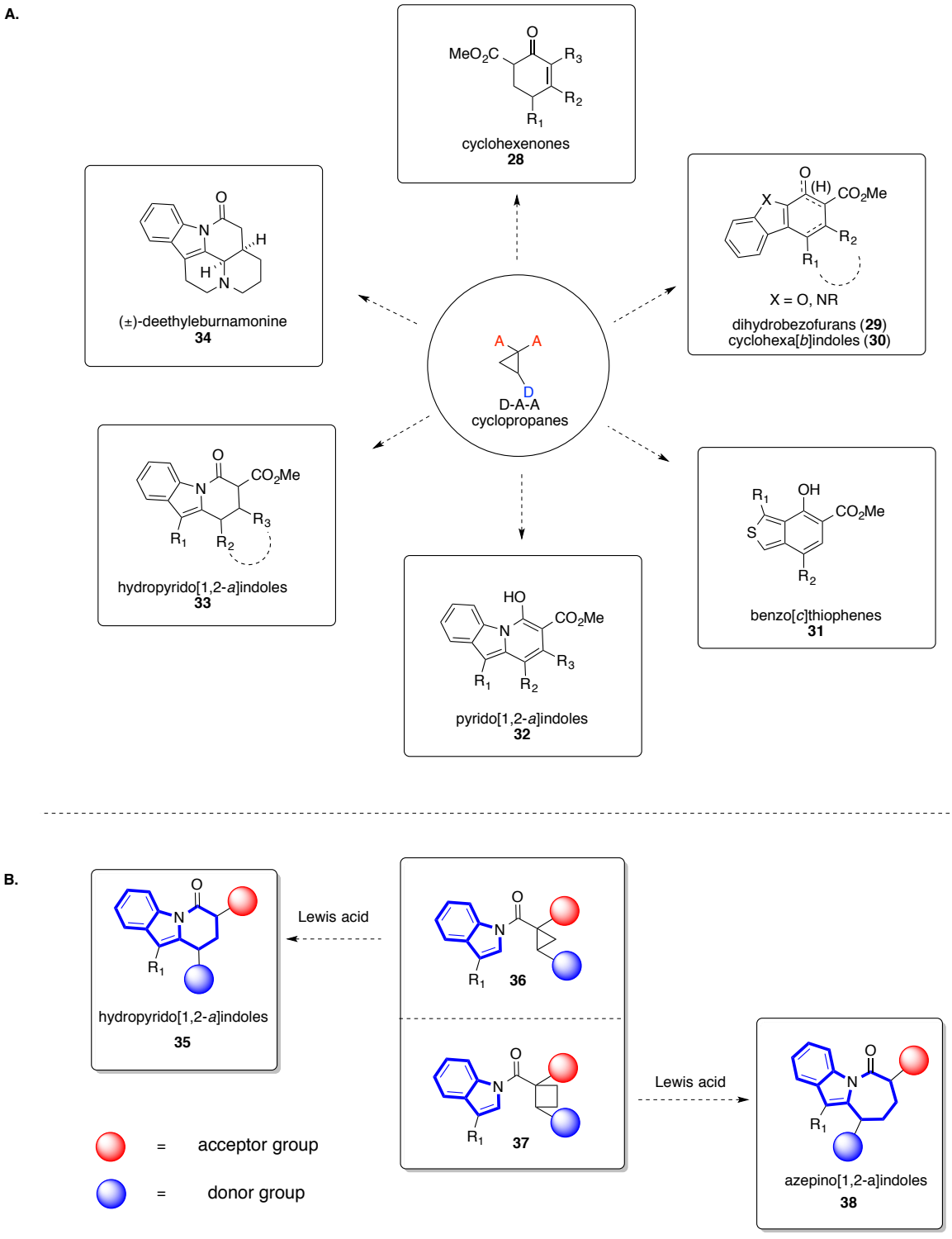


Figure 3.2. Strained Carbocycles for Access to Molecular Complexity.

As highlighted in Chapter 1, D-A-A cyclopropanes and cyclobutanes share similar reactivity profiles in many instances. Cyclopropanes, however, have traditionally received much more attention by synthetic chemists and subsequently have been more extensively incorporated in synthetic methodologies as well in the total synthesis of natural products.[18a, 19] An analysis of the chemical landscape involving these two sets of strained carbocycles demonstrates heavy investment of effort into D-A-A cyclopropanes for exploration of both their intra- and intermolecular reactivities (Figure 3.3). D-A-A cyclobutanes, on the other hand, have only recently started gaining popularity as viable synthetic precursors.[20] In this small set of publications involving D-A-A cyclobutanes, most of the focus has been on their intermolecular transformations. Intramolecular reactivity of D-A-A cyclobutanes remain largely unexplored. In fact, to the best of our knowledge, no reports involving intramolecular cycloisomerization reactions of D-A-A cyclobutanes had been reported prior to the France lab's exploration of this area. Our intended strategy for azepino[1,2-*a*]indole synthesis sought to address this deficit as well as provide an efficient and modular approach for accessing this important scaffold.

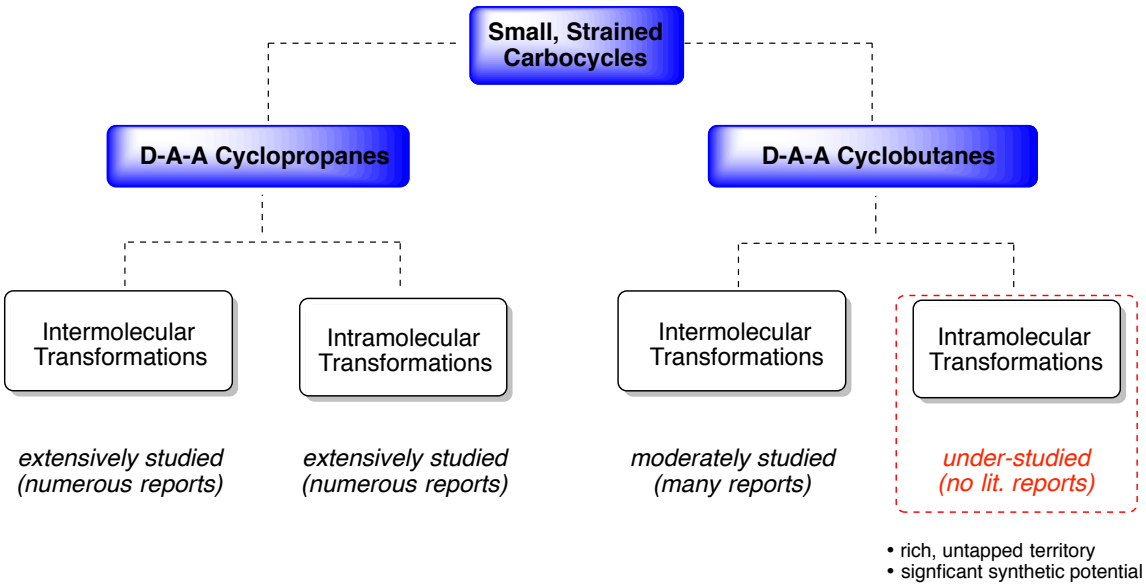
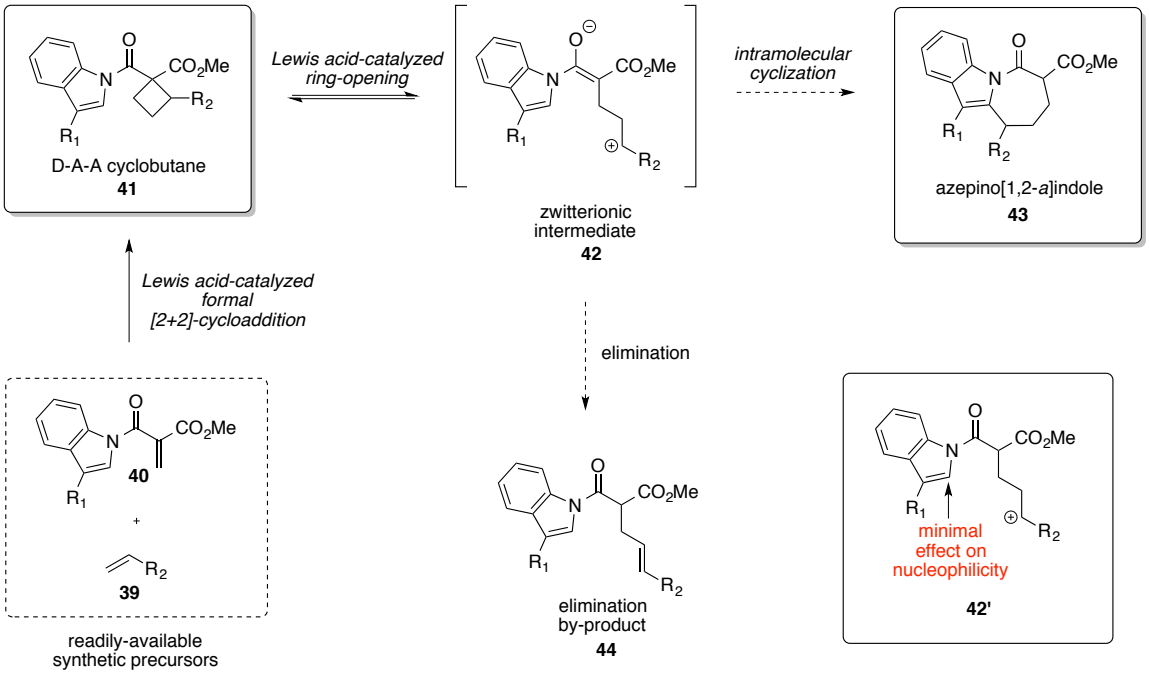


Figure 3.3. Chemical Landscape for Utilization of D-A-A Cyclopropanes and Cyclobutanes in Synthesis.

3.2.2 Reaction Design

A formal [2+2]-cycloaddition of alkylidenes **40** and alkenes **39** would conceivably produce D-A-A cyclobutanes **41** (Scheme 3.3). While the intended cycloisomerization has been demonstrated extensively for D-A-A cyclopropanes, its application to D-A-A cyclobutanes has not been explored and poses several difficulties. Firstly, formation of larger 7-membered rings (in the case of D-A-A cyclobutane reactions) is entropically less favored compared to 6-membered ring formation (in case of D-A-A cyclopropane reactions).[21] Secondly, once ring-opening occurs to form zwitterionic intermediate **42**, it is imperative that π-attack (by the heteroaromatic system) occur immediately thereafter to preclude side reactions such E1-elimination (to form alkene **44**) or any potential degradation pathways (Scheme 3.3). The chosen indole π-nucleophile is particularly suitable for this transformation since it has been demonstrated to undergo rapid and smooth reactivity in Friedel-Crafts-type transformations.[22] However, in the event that enolate protonation-tautomerization precluded cyclization,

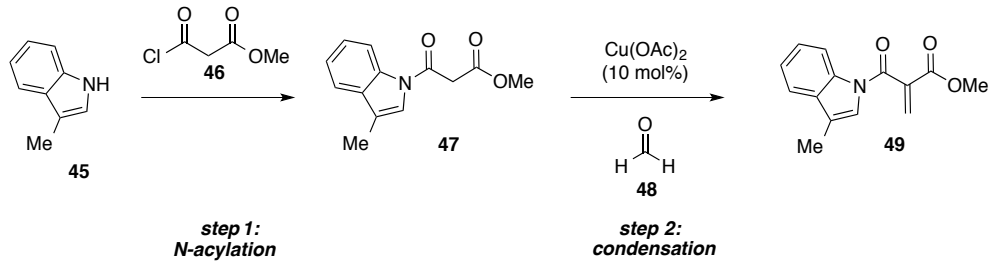
amide **42'** would be formed. Formation of this "amide" moiety would lead to some degree of de-activation of the indole ring towards the Friedel-Crafts transformation, a concern for the effectiveness of cyclization towards azepine **43**. Finally, a concern for this approach to azepinoindoles lay in the limited number of available methods of synthesizing D-A-A cyclobutanes[23] compared to D-A-A cyclopropanes.[24] This limitation, in turn, dictates that the sought after [2+2]-cycloaddition be tolerant of a variety of alkenes and alkylidenes in order to render the azepine synthesis robust.



Scheme 3.3. D-A-A Cyclobutane Strategy Towards Azepino[1,2-*a*]indole Synthesis.

3.2.3 Synthesis of Model Substrate

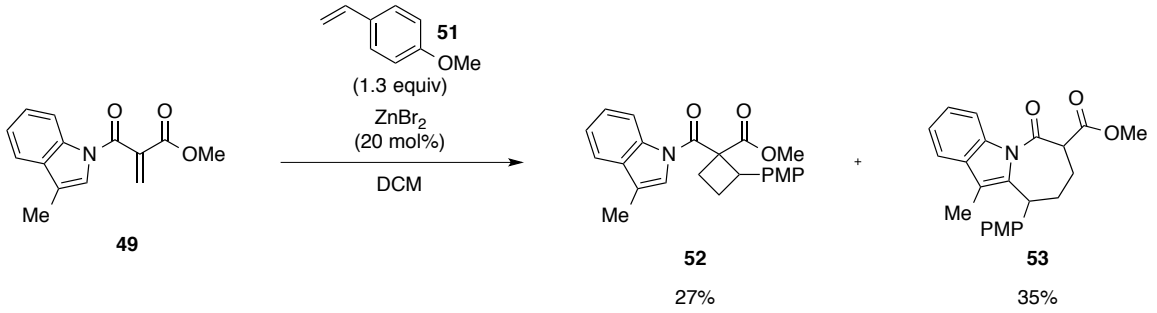
The model alkylidene, *N*-indolyl malonamide **49**, was synthesized via a straightforward, two-step sequence in which commercially-available 3-methylindole **45** was subjected to methyl malonyl chloride **46** to afford *N*-acylated indole **47** (Scheme 3.4). Indole **47** then underwent a $Cu(OAc)_2$-catalyzed condensation, in the presence of formaldehyde **48**, to furnish the desired alkylidene **49**.



Scheme 3.4. Synthesis of the Model Substrate.

3.2.4 Proof of Principle

As a starting point, we envisaged cyclobutane formation via a Lewis acid-catalyzed formal [2+2]-cycloaddition protocol established by Roberts and co-workers (Scheme 3.5).[17a] Alkylidene malonamide **49** and 4-methoxystyrene **51** were chosen as the model substrates with 20 mol% $ZnBr_2$ as the catalyst. Under these conditions, the expected D-A-A cyclobutane **52** was isolated in 27% yield. Serendipitously, azepino[1,2-a]indole **53** was also formed in the reaction in 35% yield after 24 h. This exciting result hinted at the possibility of a direct, one-pot synthesis of azepinoindoles from precursor alkenes and alkylidenes in a formal [5+2]-cycloaddition fashion.



Scheme 3.5. Serendipitous Synthesis of Azepino[1,2-*a*]indoles.

3.2.5 Reaction Optimization

Having established an initial set of conditions (20 mol% $ZnBr_2$, DCM) for the formation of D-A-A cyclobutane **52** and azepine **53** from starting materials **49** and **51**, an extensive catalyst screen was performed (Table 3.1). The goal of this optimization was to identify a catalytic system for the formation of only azepine **53** (complete suppression of cyclobutane **52**). This exclusive formation of azepine **53** would eliminate the need to isolate cyclobutane **52** and re-subject it to a further reaction optimization sequence for its cycloisomerization to azepine **53**.

First, an investigation of the effect of amount of $ZnBr_2$ loading on reaction outcome was investigated. Using 30 and 100 mol% loading led to exclusive formation of azepine **53** in 49% and 52% yield respectively (Table 3.1, entries 2, 3). Surprisingly, no change is reaction time was observed – reactions took about 24 h irrespective of the amount of $ZnBr_2$ loading. Other oxophilic Lewis acids, possessing the ability to bind to the dicarbonyl moiety of **50**, were tested. $Sc(OT)_3$ rapidly led to azepine formation in 72% yield at a loading of 20 mol% (Table 3.1, entry 4), while reducing its loading to 10 mol% afforded the same product **53** in 78% yield (Table 3.1, entry 5). Other Lewis acids,

such as $Yb(OTf)_3$, $La(OTf)_3$, and $Mg(OTf)_2$ gave either low yields of azepine **53** or mixtures of azepine **53** and cyclobutane **52** (Table 3.1, entries 6, 9, 11).

During the optimization study, it was observed that azepine product formation generally occurred in good to high diastereoselectivity, with the *cis*-product as the major diastereomer. The $ZnBr_2$ reactions gave diastereoselectivities in the range of 11:1 to 16:1 while $Yb(OTf)_3$, $La(OTf)_3$, and $Mg(OTf)_2$ gave *dr*'s of 12:1, 8:1, and 19:1 respectively. Fortunately, 10 mol% $Sc(OTf)_3$ was selected as the optimal catalyst system since afforded azepine **53** in the highest chemical yield (78%) as well as the best diastereoselectivity (33:1) (Table 3.1, entry 5).

The preference towards exclusive formation of azepine **53** under either high catalyst loadings (30 mol% and 100 mol% $ZnBr_2$) or strongly Lewis acidic metal salts, such as $Sc(OTf)_3$, suggested the possibility of cyclobutane **52** as a potential intermediate *en route* to azepinoindole **53**. Conceivably, cyclobutane **52** could cycloisomerize, under suitable reaction conditions, to yield product **53** in an irreversible fashion. Consequently, the goal of the method was modified to focus on a direct, formal [5+2]-cycloaddition of alkylidenes, of the type **50**, and alkenes such as **51** for synthesis of azepines exemplified by **53**.

Table 3.1. Lewis Acid Screen for Formal [5+2]-Cycloaddition[a].

entry	Lewis acid	Loading (mol%)	time (h)	combined yield[b] (%)	**52** : **53**[c]	*dr*[d]
1	$ZnBr_2$	20	24	62	1 : 1.3	11 : 1
2	$ZnBr_2$	30	24	49	0 : 1	16 : 1
3	$ZnBr_2$	100	24	52	0 : 1	14 : 1
4	$Sc(OTf)_3$	20	1	72	0 : 1	11 : 1
5	$Sc(OTf)_3$	10	2	78	0 : 1	33 : 1
6	$Yb(OTf)_3$	10	7	44	1 : 1.3	12 : 1
7	$In(OTf)_3$	10	0.5	--	--	-- [e]
8	$Al(OTf)_3$	10	0.5	--	--	-- [e]
9	$La(OTf)_3$	10	7	25	1.6 : 1	8 : 1
10	$Ga(OTf)_3$	10	0.5	--	--	-- [e]
11	$Mg(OTf)_2$	10	48	25	0 : 1	19 : 1
12	$Zn(OTf)_2$	10	24	--	--	-- [e]
13	$Cu(OTf)_2$	10	24	--	--	-- [e]
14	$Ni(OTf)_2$	10	24	--	--	-- [e]

[a] Reaction run with 1 equiv of **49**, 1.3 equiv of **51**, and x mol% Lewis acid at room temp in DCM (0.17 M). [b] Isolated yield after column chromatography. [c] Ratio on isolated yield. [d] Diastereomeric ratio of azeopinoindole product. [e] Degradation or side products observed

Next, a solvent screen was carried out. Weakly coordinating, non-polar solvents such as PhH, PhMe, and DCM proved competent and a led to product formation in 64%, 57%, and 78% yield respectively (Table 3.2, entries 1, 5, 6). On the other hand, polar coordinating solvents led to either low reaction yields (32% yield with EtOAc), or no product formation at all (with MeCN and THF) (Table 3.2, entries 2, 3, 4). It is likely that coordinating solvents bind to the metal center of the catalyst leading to either alteration in Lewis acidity or complete sequestration thus hindering desired reactivity. Attempts to alter reaction concentration and temperature were unfruitful and did not lead to any improvement in either chemical yield or diastereoselectivity.

Table 3.2. Solvent Screen for Azepino[1,2-*a*]indole Synthesis[a].

entry	Solvent	time (h)	yield of **53**[b] (%)
1	PhH	4.5	64
2	MeCN	2	--[c]
3	THF	72	--[d]
4	EtOAc	24	32
5	PhMe	4.5	57
6	DCM	2	78

[a] Reaction run with 1 equiv of **49** and 1.3 equiv of **51** at room temp in DCM (0.17 M) using 10 mol% $Sc(OTf)_3$. [b] Isolated yield after column chromatography. [c] Side products observed. [d] Decomposition products observed.

3.2.6 Reaction Scope and Limitations

Using 10 mol% $Sc(OTf)_3$ as the optimal catalyst, an investigation of the scope of the direct, formal [5+2]-cycloaddition was commenced (Figure 3.4, A). First, an exploration of the reactivity of alkylidene **49** with various mono-substituted alkenes **54** was probed. *Para*-substituted styrenes led to azepines **53a**-**53d**, with the more electron-rich styrenes leading to higher yields. The highly electron-deficient alkene, *para*-nitrostyrene, did not afford any desired product (**53e**) at all. This trend pointed towards a carbocation-type mechanism in which a build-up of positive charge on the benzylic position is experienced during the reaction.

Using ortho-methoxy styrene in the reaction did not lead to any product whereas *ortho*-bromostyrene azepine **53g** in a low yield (15%). Further investigation revealed that 2-4-dimethoxystyrene and 2-bromo-4-methoxystyrene were tolerated in this transformation and affords azepinoindoles **53h** and **53i** in 25% and 66% yield respectively. These results highlight some subtle stereoelectronic sensitivity of the formal [5+2]-cycloaddition. Bulky *ortho* substituents on styrene were not tolerated although this

effect is somewhat mitigated by installing an electron-donating *para*-substituent. Presumably, this installation of a *p*-methoxy group leads to a boost in nucleophilicity of the ortho-substituted styrene thus forcing the desired cycloaddition.

Other alkenes, such as 2-vinyl naphthalene, 2-vinyl furan and phenyl vinyl sulfide were well-tolerated and led to azepino[1,2-*a*]indoles **53j-53l** in 45%, 62%, and 85% respectively. Interestingly, use of ethyl vinyl ether in the reaction did not lead to the desired product; starting material **49** was recovered. Ethyl vinyl ether, being highly electron-rich, easily degrades/polymerizes in the presence of strong Lewis acids.[25] Upon being subjected to the milder $Yb(OTf)_3$ catalyst, cyclobutane **52a** was formed, albeit in low yield (Figure 3.4, B). Finally, re-subjecting D-A-A cyclobutane **52a** to the optimized Sc-conditions led to unsaturated azepine **53m** in 81% yield. The unsaturation in **53m** presumably results from a Lewis acid-mediated EtOH elimination on the ethoxy-substituted azepine intermediate **53m'**. In addition, exploration of multi-substituted alkenes as well substituted indole-based alkylidenes produced products in **53n-53s** in 54-92% yield.

Unfortunately, 1-hexene and allyltrimethylsilane proved weak nucleophiles for the cycloaddition transformation; respective products **53t** and **53u** were not observed. Other unsuccessful reactions involved tri-substituted alkylidenes for the formation of azepines **53v** and **53w**. Such substitution likely stalls the formal [5+2]-cycloaddition due to steric hindrance. Finally, *N*-based alkenes were also not tolerated (degradation and polymerization observed), thus azepinoindole **53x** proved elusive via this methodology.

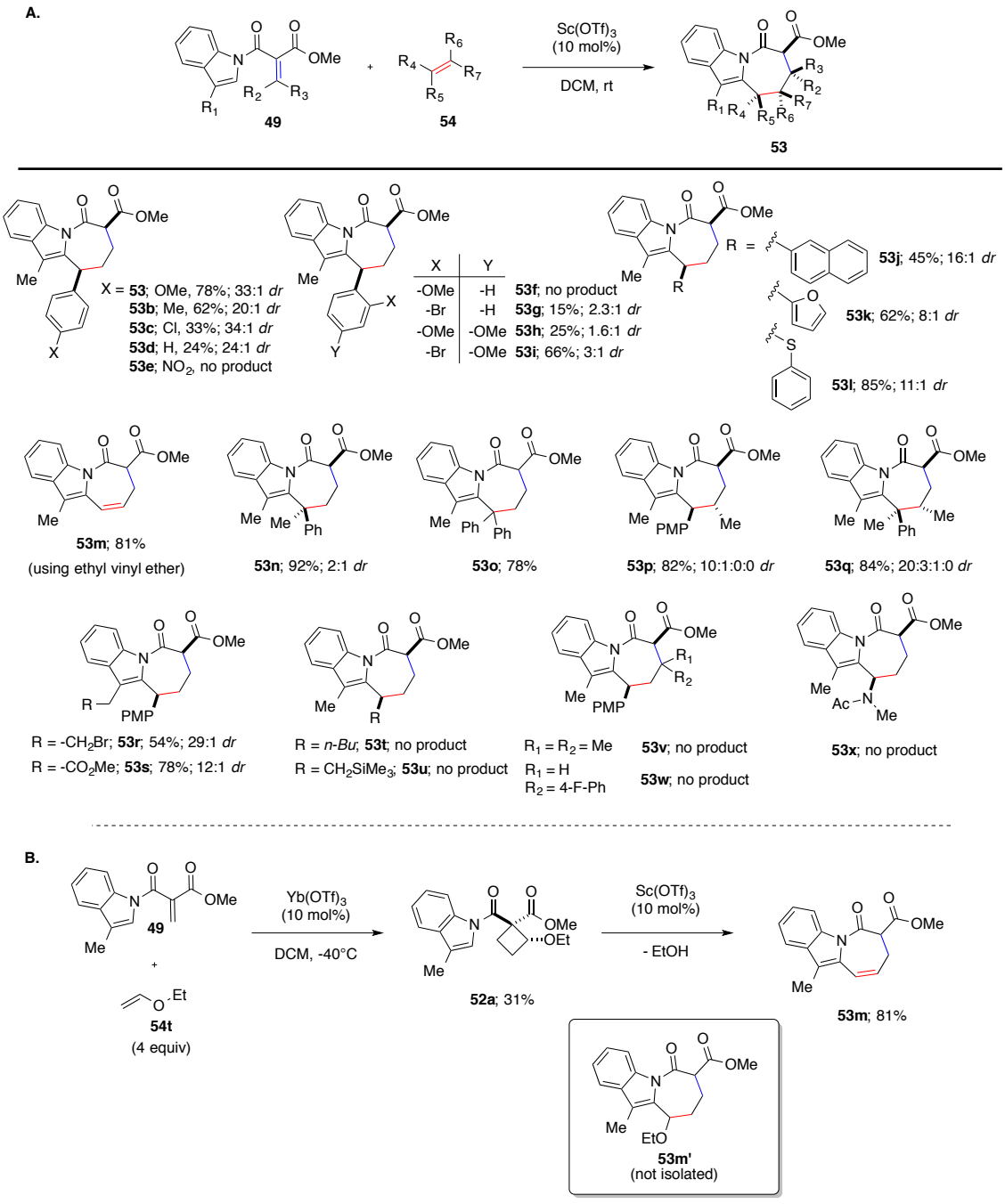


Figure 3.4. Scope for Azepino[1,2-*a*]indole Synthesis.

3.2.7 Reaction Mechanism

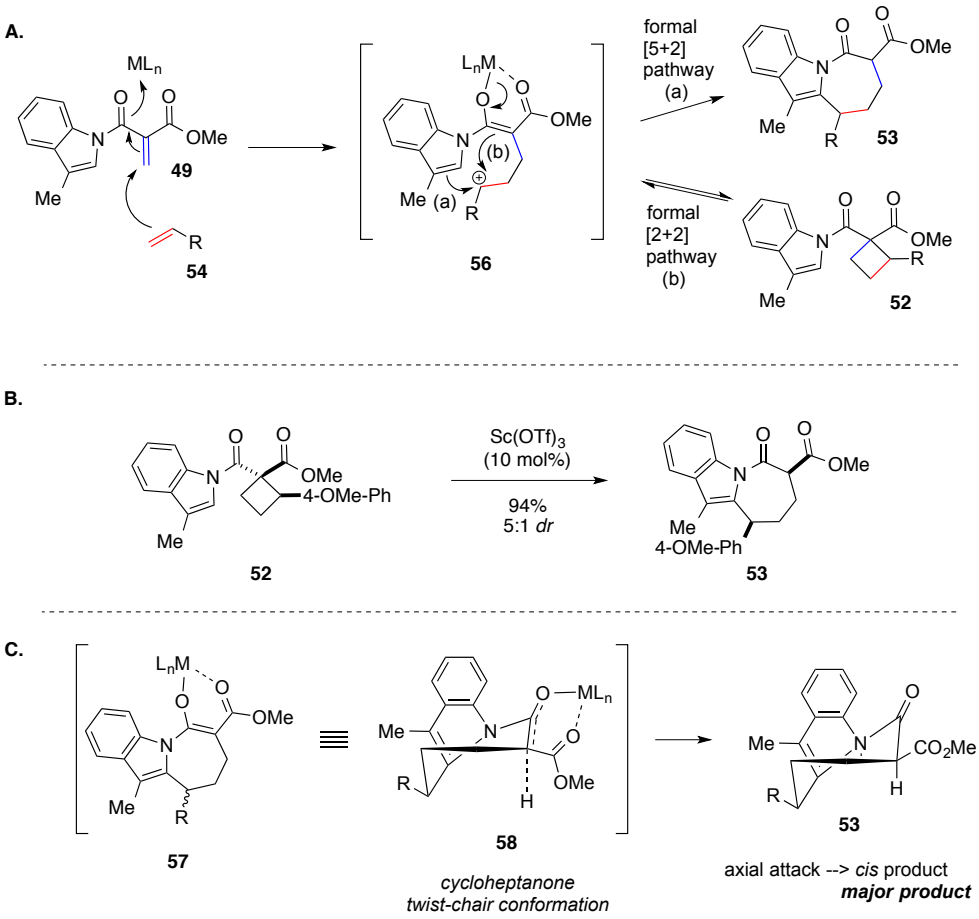
Mechanistically, this transformation likely proceeds via an initial Lewis acid-catalyzed π-type Michael addition of alkene **54** onto alkylidene **49**, forming zwitterionic

intermediate **I** (Scheme 3.6, A). Intermediate **56** can undergo two parallel pathways: (a) a formal [5+2] cycloaddition to form the desired azepine **53**, or (b) a formal [2+2] cycloaddition to furnish the donor-acceptor cyclobutane **52**. Given entropic considerations for ring-forming reactions,[21] it is likely that the transformation proceeds via the cyclobutane first, followed by a cycloisomerization to give the azepino[1,2-*a*]indole. Isolating cyclobutane **52** and subjecting it to the reaction conditions smoothly gave **53** in 94% yield with 50:1 *dr* (Scheme 3.6, B). This result supports the proposed mechanism (Scheme 3.6, A) and also represents the first literature example of intramolecular ring-opening/cyclization of a donor-acceptor cyclobutane.

The mechanism proposed for the [5+2]-cycloadditions invokes a polar, step-wise sequence of events. Evidence for a stepwise mechanism seems to be supported by several factors: (1) the reaction appears to favor electron-rich alkenes pointing towards the importance of a nucleophilic attack onto alkylidenes **49** via Michael addition-type pathway; (2) for styrene Michael donors, the highest yields were obtained with resonance stabilizing *para*-substituents (such –OMe) or alpha-substituents (such as –Me or –Ph) suggesting the formation of a benzylic carbocation during the reaction; (3) high steric sensitivity – substituents on the vinyl position of alkylidenes **49** as well as tetrasubstituted Michael donors are not tolerated at all presumably due to preclusion of the initial Michael addition step. These factors, among others, have also been reported as evidence for step-wise mechanisms in other cycloadditions in literature.[26] More definitive evidence of a polar or conservative mechanism could be gathered through use of a purely *E*- or *Z*-alkene in the reaction. In each case, maintenance of relative stereochemistry in the

azepine would suggest a concerted mechanism while stereochemical scrambling would support a polar one.

Most of the substrates investigated in this study yielded corresponding azepino[1,2-*a*]indoles with high degrees of diastereoselection. Presumably, relative stereochemistry is set during the protonation step, after 7-membered ring formation. The Lewis acid-azepino[1,2-*a*]indole enolate complex (**57**) is expected to adopt a twist-chair conformation similar to that of cycloheptenone-type systems (Scheme 3.6, C).[27] A preferred pseudoaxial protonation (**58**) leads to the *cis* product as the major diastereomer. Notably, this kinetic protonation also places the two bulky groups (-R and $-CO_2Me$) in thermodynamically favored pseudoequatorial positions. As such, the *cis*-diastereomers are formed as the thermodynamic products.

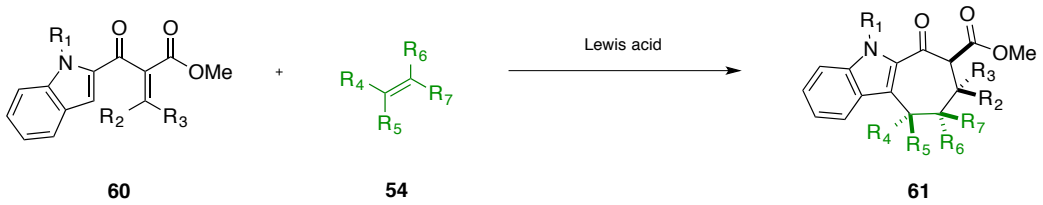


Scheme 3.6. Mechanism for Azepino[1,2-*a*]indole Synthesis.

3.3 Development of a Formal [5+2] Approach to Cyclohepta[*b*]indoles

3.3.1 Reaction Design

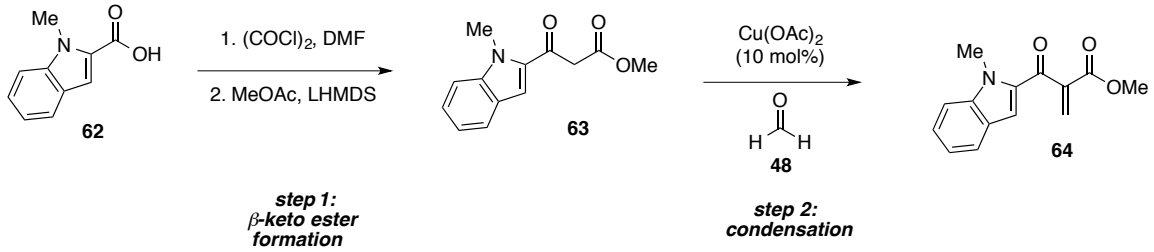
In an effort to extend it to synthesis of scaffolds other than the azepino[1,2-*a*]indoles, the formal [5+2]-cycloaddition strategy could conceivably be applied to *C*-acyl alkylidenes, of the type **60** (Scheme 3.7). Such an application would lead to cyclohepta[*b*]indoles (**61**), another prominent scaffold in the indole alkaloid family of natural products. Just as in the case of azepino[1,2-*a*]indoles (discussed in the previous section), substitutions on the starting materials **60** and **54** could presumably be effected, in a modular fashion, to afford variously functionalized cyclohepta[*b*]indoles.



Scheme 3.7. Formal [5+2]-Cycloaddition Approach to Cyclohepta[*b*]indoles.

3.3.2 Synthesis of Model Substrate

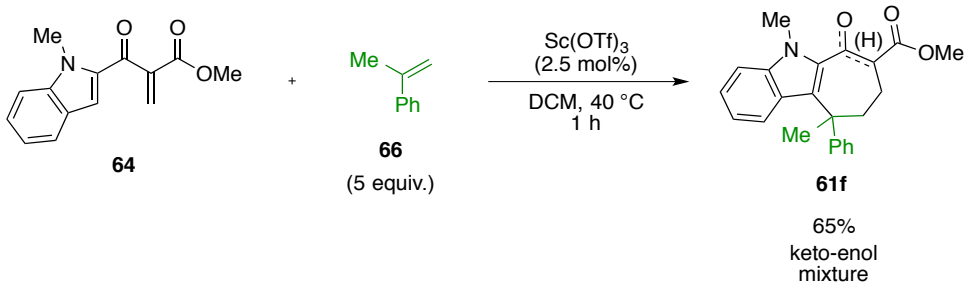
The model substrate, **64**, was synthesized via a three-step sequence shown in Scheme 3.8. *N*-methyl indole-2-carboxylic acid **62** was subjected to oxalyl chloride and catalytic DMF to form *N*-methyl indole-2-carbonyl chloride *in situ* (Scheme 3.8). To this acid chloride was added the enolate of methyl acetate, leading to beta-keto ester **63**. Finally, a $Cu(OAc)_2$-catalyzed condensation of beta-keto ester **63** with formaldehyde yielded model alkylidene **64**.



Scheme 3.8. Synthesis of the Model Substrate.

3.3.3 Proof of Principle

Subjecting alkylidene **64** and α-methyl styrene **66** to catalytic Sc-conditions afforded cyclohepta[*b*]indole **61f** in 65% yield as a mixture of keto-enol tautomers (Scheme 3.9). This example demonstrated the applicability of the formal [5+2]-cycloaddition strategy towards chemotypes other than the azepinoindole scaffold. Only a 2.5 mol% loading of $Sc(OTf)_3$ was required for complete conversion, a notable feature of this transformation.



Scheme 3.9. Cyclohepta[*b*]indole Synthesis via a Formal [5+2]-Cycloaddition.

3.3.4 Reaction Optimization

A Lewis acid screen of oxophilic metals salt revealed the range of catalysts able to promote this transformation. Notable metal salts included $Hf(OTf)_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Al(OTf)_3$ which all gave yields above 50% (Table 3.3, entries 1-3, 5). Gratifyingly, a 1:1 mole ratio of $Ca(NTf_2)_2$:$(n\text{-}Bu)_4NPF_6$ provided the highest chemical yield (78%) (Table 3.3, entry 10). This $Ca(NTf_2)_2$/$(n\text{-}Bu)_4NPF_6$ mixture, developed by Leonori and co-workers, presumably undergoes a ligand metathesis, producing $Ca(NTf_2)(NPF_6)$, a strongly Lewis acidic and highly oxophilic metal complex.[28] This $Ca(NTf_2)(NPF_6)$ complex is thus effective for binding dicarbonyl systems of the type **64**, which initiates the formal [5+2]-cycloaddition. Notably, neither $Ca(NTf_2)_2$ nor $(n\text{-}Bu)_4NPF_6$ alone promoted the reaction at all, justifying the importance of a combination of the two (Table 3.3, entry 11, 12). The success of the Ca-based metal salt in promoting this transformation was a major advantage towards sustainability due to its: (1) low cost; (2) low toxicity; and (3) ease of disposal.[28]

It should be noted that all reaction times in this study were relatively short; complete conversions were observed in a 0.5-1.5 h time ranges. Efforts to optimize temperature, reaction concentration, and equivalents of α-methyl styrene did not lead to any improvement in chemical yield.

Table 3.3. Lewis Acid Screen for Cyclohepta[*b*]indole Synthesis[a].

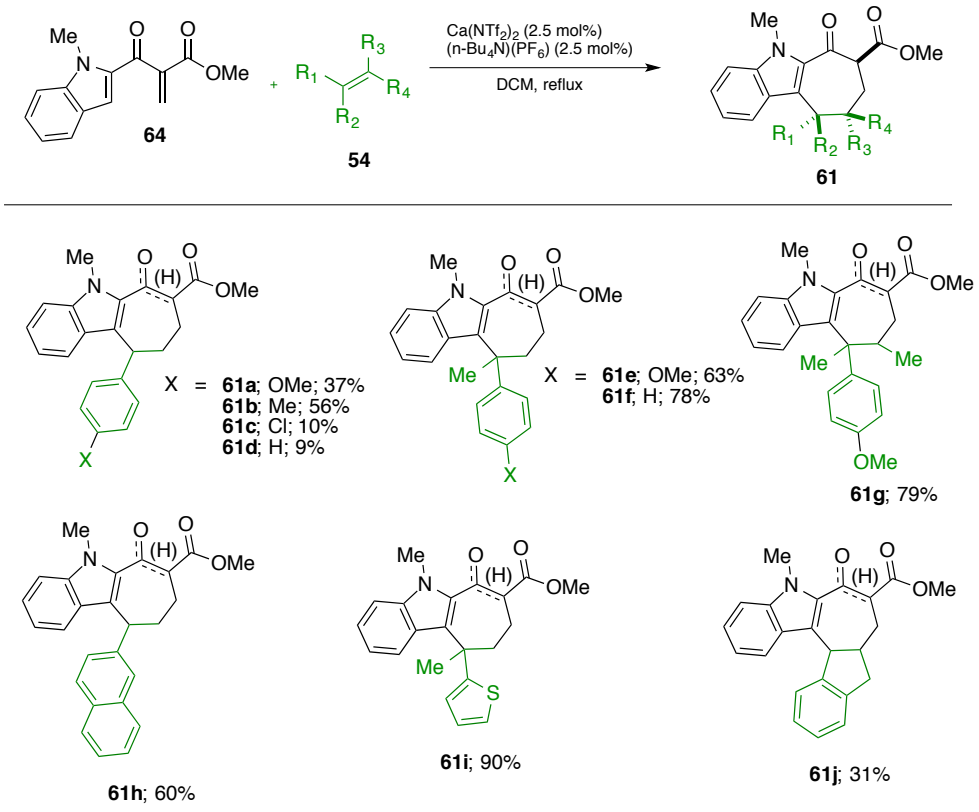
entry	Lewis acid	time (h)	Yield of **61f**[b] (%)
1	$Hf(OTf)_4$	0.5	73
2	$Sc(OTf)_3$	1	65
3	$Yb(OTf)_3$	1	51
4	$In(OTf)_3$	1	43
5	$Al(OTf)_3$	1	73
6	$La(OTf)_3$	1	33
7	$Zn(OTf)_2$	1.5	31
8	$ZnBr_2$	1	42
9	$Cu(OTf)_2$	0.5	44
10	$Ca(NTf_2)_2$ $(n\text{-}Bu)_4NPF_6$	0.5	78
11	$Ca(NTf_2)_2$	24	-- [c]
12	$(n\text{-}Bu)_4NPF_6$	24	-- [c]

[a] Reaction run with 1 equiv of **64**, 5 equiv of **66**, and 2.5 mol% Lewis acid at 40 °C in DCM (0.1 M). [b] Isolated yield after column chromatography. [c] No reaction, starting material recovered.

3.3.5 Reaction Scope and Limitations

Formal [5+2]-cycloadditions using alkylidene **64** and variety of alkenes were investigated (Scheme 3.10). Different *para*-substituted styrenes led to cyclohepta[*b*]indoles **61a-61d**. Unfortunately, under the reaction conditions, significant degradation and polymerization of the styrenes were observed leading to unpredictable, haphazard yields. Di- and tri-substituted alkenes proved better-behaved, leading to cyclohepta[*b*]indoles **61e**, **61f**, **61g** and **61i** in 63%, 78%, 79%, and 90% yields. The reaction with indene provided cyclohepta[*b*]indole **61j**, albeit in a lowered yield (31%).

Investigation of the full scope of this methodology is still ongoing and diastereoselectivities of all products are yet to be determined (via Krapcho derivatizations of formed keto-esters **61**).



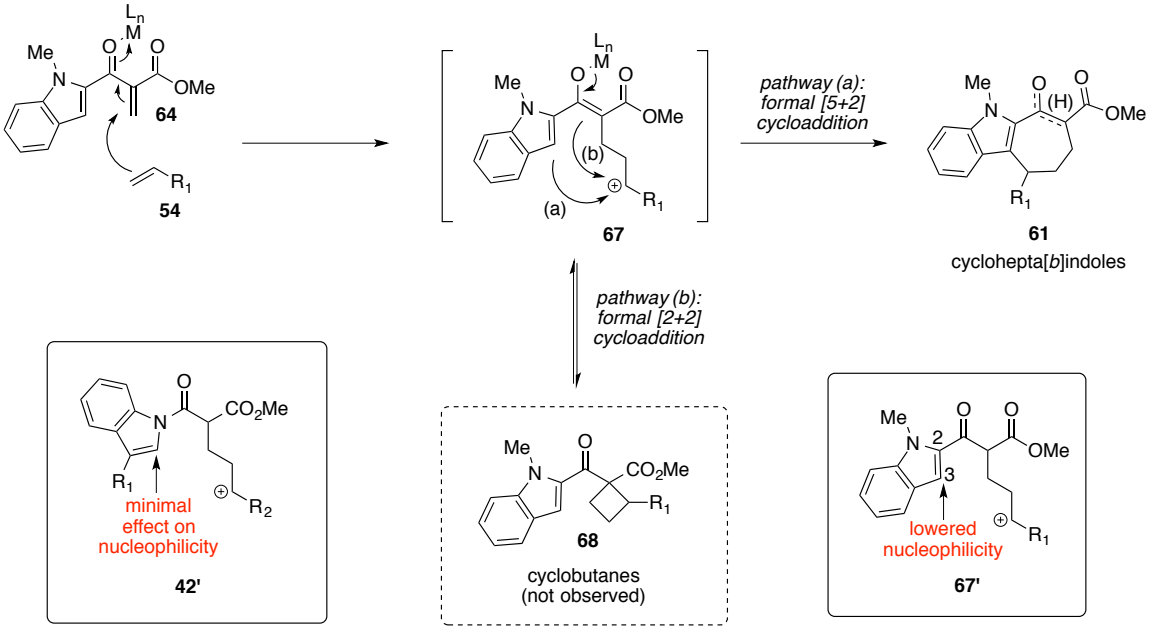
Scheme 3.10. Substrate Scope for Cyclohepta[*b*]indole Synthesis.

3.3.6 Reaction Mechanism

An initial π-type Michael addition of alkene **54** onto alkylidene **64** affords 1,4-zwitterionic intermediate **67** (Scheme 3.11). Subsequent π-attack on the carbocation (pathway (a): formal [5+2]-cycloaddition) forms the desired cyclohepta[*b*]indoles **61**. Alternatively, pathway (b) – formal [2+2]-cycloaddition, would afford the more entropically-accessible D-A-A cyclobutanes **68**. However, no cyclobutanes were observed in this study. Although they may transiently be formed in this transformation,

D-A-A cyclobutanes **68** are likely unstable under the reaction conditions (due to the strongly polarizing keto group) and thus rapidly cycloisomerize to the cyclohepta[*b*]indoles **61**.

Generally, the formal [5+2]-cycloaddition strategy for the synthesis of cyclohepta[*b*]indoles led to lowered yields with respect to azepino[1,2-*a*]indoles. This disparity can the attributed to ketone **67'**, formed upon protonation-tautomerization of **67** prior to cyclization. Reduced nucleophilicity at C-3 of indole by the keto group in **67'** would potentially lead to inefficient cyclization as well as promotion of side reactivity such as E1-elimination. This effect is likely minimal in case of azepinoindole synthesis where *N*-electrons in **42'** are less effectively delocalized into the carbonyl system leading to minimal reduction in the nucleophilicity of the indole π-system.

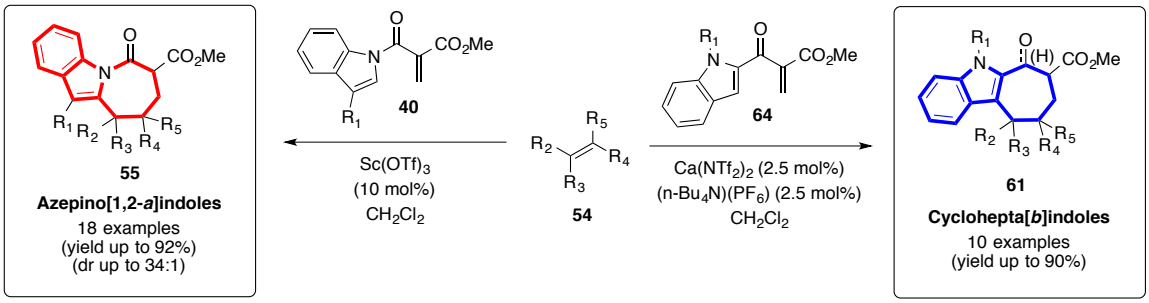


Scheme 3.11. Reaction Mechanism for Cyclohepta[*b*]indole Synthesis.

3.4 Summary: Formal [5+2]-Cycloadditions for Synthesis of Azepino[1,2-*a*]indoles and Cyclohepta[*b*]indoles

Azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles are prominent scaffolds in the indole alkaloid family of natural products. Presented in this chapter is a versatile formal [5+2]-cycloaddition strategy for access to these important scaffolds (Scheme 3.12). Indole-based alkylidenes **40** or **64** and alkenes **54** react in the presence of appropriate Lewis acids leading to the desired 7-membered rings. Experimental evidence appears to indicate that these formal [5+2]-cycloadditions are not concerted and occur via a polar, stepwise mechanism. Furthermore, variations in the alkylidenes and alkenes can be performed in a modular fashion leading to broad substrate scope under mild reaction conditions.

In the process of developing these methods, evidence was gathered for the existence of D-A-A cyclobutanes as intermediates in the formal [5+2]-cycloadditions. Our lab has continually been interested in strained carbocycles: cyclopropanes and cyclobutanes. As discussed in Chapter 1, D-A-A cyclobutanes are an emerging class of versatile building blocks whose intermolecular reactivity has been of great interest. The discovery of putative D-A-A cyclobutane intermediates triggered their ring-opening cyclization to the respective azepino[1,2-*a*]indoles. Importantly, this transformation represented the first literature example of cycloisomerization of a D-A-A cyclobutane in literature and thus, hopefully, will spark similar cycloisomerizations going forward.



Scheme 3.12. Formal [5+2]-Cycloadditions for Synthesis of Azepino[1,2-*a*]indoles and Cyclohepta[*b*]indoles.

3.5 EXPERIMENTAL SECTION

- For supporting information (including characterization) for the synthesis of azepino[1,2-*a*]indoles see: Shenje, R.; Martin, M. C.; France, S., A Catalytic Diastereoselective Formal [5+2] Cycloaddition Approach to Azepino[1,2-*a*]indoles: Putative Donor–Acceptor Cyclobutanes as Reactive Intermediates. *Angew. Chem. Int. Ed.* **2014,** *53* (50), 13907-13911.
- Cyclohepta[*b*]indoles **61** synthesized by Martin, M. C. as part of a manuscript in progress: Shenje, R.; Martin, M. C.; France, S., Catalytic Formal [5+2]-Cycloadditions for Cyclohepta[*b*]indole synthesis. *Manuscript in Preparation*, *To be Published*.

3.6 REFERENCES

1. Shenje, R.; Martin, M. C.; France, S., A Catalytic Diastereoselective Formal [5+2] Cycloaddition Approach to Azepino[1,2-*a*]indoles: Putative Donor–Acceptor Cyclobutanes as Reactive Intermediates. *Angew. Chem. Int. Ed.* **2014,** *53* (50), 13907-13911.

2. (a) Ryan, K. S.; Moore, B. S., Alkaloid biosynthesis takes root. *Nat. Chem. Biol.* **2009,** *5* (3), 140-141; (b) Cordell, G. A., *The alkaloids: chemistry and biology*. Academic Press: **2008**; Vol. 65; (c) Gul, W.; Hamann, M. T., Indole alkaloid marine natural products: An established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases. *Life Sci.* **2005,** *78* (5), 442-453; (d) Hillwig, M. L.; Zhu, Q.; Liu, X., Biosynthesis of ambiguine indole alkaloids in cyanobacterium Fischerella ambigua. *ACS Chem. Biol.* **2013,** *9* (2), 372-377.

3. Galliford, C. V.; Scheidt, K. A., Pyrrolidinyl‐Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem. Int. Ed.* **2007,** *46* (46), 8748-8758.

4. (a) Liu, Q.; Jia, Y., Total synthesis of (+)-lysergic acid. *Org. Lett.* **2011,** *13* (18), 4810-4813; (b) Liu, Q.; Zhang, Y.-A.; Xu, P.; Jia, Y., Total synthesis of (+)-lysergic acid. *J. Org. Chem.* **2013,** *78* (21), 10885-10893; (c) Oppolzer, W.; Francotte, E.; Bättig, K., Total Synthesis of (±)‐Lysergic Acid by an Intramolecular Imino‐Diels‐Alder Reaction. Preliminary communication. *Helv. Chim. Acta* **1981,** *64* (2), 478-481; (d) Umezaki, S.; Yokoshima, S.; Fukuyama, T., Total Synthesis of Lysergic Acid. *Org. Lett.* **2013,** *15* (16), 4230-4233; (e) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B., The total synthesis of lysergic acid. *J. Am. Chem. Soc.* **1956,** *78* (13), 3087-3114.

5. (a) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L., Total synthesis of vinblastine, vincristine, related natural

products, and key structural analogues. *J. Am. Chem. Soc.* **2009,** *131* (13), 4904-4916; (b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T., Stereocontrolled total synthesis of (+)-vinblastine. *J. Am. Chem. Soc.* **2002,** *124* (10), 2137-2139.

6. (a) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H., An Efficient Approach to Aspidosperma Alkaloids via [4+ 2] Cycloadditions of Aminosiloxydienes: Stereocontrolled Total Synthesis of (±)-Tabersonine. Gram-Scale Catalytic Asymmetric Syntheses of (+)-Tabersonine and (+)-16-Methoxytabersonine. Asymmetric Syntheses of (+)-Aspidospermidine and (-)-Quebrachamine. *J. Am. Chem. Soc.* **2002,** *124* (17), 4628-4641; (b) Ziegler, F. E.; Bennett, G. B., Claisen rearrangement in indole alkaloid synthesis. Total synthesis of (±)-tabersonine. *J. Am. Chem. Soc.* **1973,** *95* (22), 7458-7464.

7. Bonjoch, J.; Solé, D., Synthesis of strychnine. *Chem. Rev.* **2000,** *100* (9), 3455-3482.

8. (a) Rijhwani, S. K.; Shanks, J. V., Effect of elicitor dosage and exposure time on biosynthesis of indole alkaloids by Catharanthus roseus hairy root cultures. *Biotechnol. Progr.* **1998,** *14* (3), 442-449; (b) DeLuca, V.; Balsevich, J.; Tyler, R. T.; Eilert, U.; Panchuk, B. D.; Kurz, W. G. W., Biosynthesis of indole alkaloids: developmental regulation of the biosynthetic pathway from tabersonine to vindoline in Catharanthus roseus. *J. Plant Physiol.* **1986,** *125* (1), 147-156.

.9. (a) Dethe, D. H.; Erande, R. D.; Dherange, B. D., Remarkable Switch of Regioselectivity in Diels–Alder Reaction: Divergent Total Synthesis of Borreverine, Caulindoles, and Flinderoles. *Org. Lett.* **2014,** *16* (10), 2764-2767; (b) Kim, J.; Movassaghi, M., Biogenetically inspired syntheses of alkaloid natural products. *Chem. Soc. Rev.* **2009,** *38* (11), 3035-3050; (c) Martin, S. F., Evolution of the vinylogous Mannich reaction as a key construction for alkaloid synthesis. *Acc. Chem. Res.* **2002,** *35* (10), 895-904; (d) Rigby, J. H.; Burke, P. J., Synthesis of highly substituted indole

alkaloid species via [4+ 1] cyclization of nucleophilic carbenes and indole isocyanates. *Heterocycles* **2006,** *67* (2), 643-653; (e) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F., Iridium-Catalyzed, Silyl-Directed Borylation of Nitrogen-Containing Heterocycles. *J. Am. Chem. Soc.* **2010,** *132* (12), 4068-4069; (f) Stowers, K. J.; Fortner, K. C.; Sanford, M. S., Aerobic Pd-catalyzed sp3 C− H olefination: a route to both N-heterocyclic scaffolds and alkenes. *J. Am. Chem. Soc.* **2011,** *133* (17), 6541-6544; (g) Vanecko, J. A.; Wan, H.; West, F. G., Recent advances in the Stevens rearrangement of ammonium ylides. Application to the synthesis of alkaloid natural products. *Tetrahedron* **2006,** *62* (6), 1043-1062; (h) Zhang, D.; Song, H.; Qin, Y., Total synthesis of indoline alkaloids: a cyclopropanation strategy. *Acc. Chem. Res.* **2011,** *44* (6), 447-457.

10. Achenbach, H.; Lottes, M.; Waibel, R.; Karikas, G. A.; Correa, M. D.; Gupta, M. P., Alkaloids and other compounds from Psychotria correae. *Phytochemistry* **1995,** *38* (6), 1537-1545.

11. Bennasar, M. L.; Vidal, B.; A. Sufi, B.; Bosch, J., Formal stereoselective synthesis of (±)-akagerine. *Chem. Commun.* **1998,** (23), 2639-2640.

12. Beaulieu, C.; Guay, D.; Wang, Z.; Leblanc, Y.; Roy, P.; Dufresne, C.; Zamboni, R.; Berthelette, C.; Day, S.; Tsou, N.; Denis, D.; Greig, G.; Mathieu, M.-C.; O'Neill, G., Identification of prostaglandin D2 receptor antagonists based on a tetrahydropyridoindole scaffold. *Bioorg. Med. Chem. Lett.* **2008,** *18* (8), 2696-2700.

13. Zhu, G.; Conner, S. E.; Zhou, X.; Chan, H.-K.; Shih, C.; Engler, T. A.; Al-awar, R. S.; Brooks, H. B.; Watkins, S. A.; Spencer, C. D.; Schultz, R. M.; Dempsey, J. A.; Considine, E. L.; Patel, B. R.; Ogg, C. A.; Vasudevan, V.; Lytle, M. L., Synthesis of 1,7-annulated indoles and their applications in the studies of cyclin dependent kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2004,** *14* (12), 3057-3061.

14. Gentles, R. G.; Zheng, X.; Ding, M.; Tu, Y.; Han, Y.; Hewawasam, P.; Kadow, J. F.; Bender, J. A.; Yeung, K. S.; Grant-Young, K. A., Compounds for the Treatment of Hepatitis C. Google Patents: **2008**.

15. (a) Bennasar, M. L.; Vidal, B.; Bosch, J., A synthetic route to the alkaloids of the ervatamine group. First total synthesis of (±)-6-oxo-16-episilicine. *Chem. Commun.* **1996,** (24), 2755-2756; (b) Amat, M.; Llor, N.; Checa, B.; Molins, E.; Bosch, J., A Synthetic Approach to Ervatamine-Silicine Alkaloids. Enantioselective Total Synthesis of (−)-16-Episilicine. *J. Org. Chem.* **2010,** *75* (1), 178-189; (c) Bennasar, M. L.; Vidal, B.; Lázaro, A.; Kumar, R.; Bosch, J., A short route for the construction of the tetracyclic ring system of silicine-methuenine alkaloids. *Tetrahedron Lett.* **1996,** *37* (20), 3541-3544.

16. (a) Faust, R.; Garratt, P. J.; Jones, R.; Yeh, L.-K.; Tsotinis, A.; Panoussopoulou, M.; Calogeropoulou, T.; Teh, M.-T.; Sugden, D., Mapping the Melatonin Receptor. 6. Melatonin Agonists and Antagonists Derived from 6H-Isoindolo[2,1-*a*]indoles, 5,6-Dihydroindolo[2,1-*a*]isoquinolines, and 6,7-Dihydro-5H-benzo[*c*]azepino[2,1-*a*]indoles. *J. Med. Chem.* **2000,** *43* (6), 1050-1061; (b) Rivara, S.; Mor, M.; Silva, C.; Zuliani, V.; Vacondio, F.; Spadoni, G.; Bedini, A.; Tarzia, G.; Lucini, V.; Pannacci, M.; Fraschini, F.; Plazzi, P. V., Three-Dimensional Quantitative Structure−Activity Relationship Studies on Selected MT1 and MT2 Melatonin Receptor Ligands: Requirements for Subtype Selectivity and Intrinsic Activity Modulation. *J. Med. Chem.* **2003,** *46* (8), 1429-1439; (c) Gritsch, P. J.; Stempel, E.; Gaich, T., Enantioselective Synthesis of Cyclohepta [*b*] indoles: Gram-Scale Synthesis of (S)-SIRT1-Inhibitor IV. *Org. Lett.* **2013,** *15* (21), 5472-5475; (d) Goswami, P.; Borah, A. J.; Phukan, P., Formation of Cyclohepta [*b*] indole Scaffolds via Heck Cyclization: A Strategy for Structural Analogues of Ervatamine Group of Indole Alkaloid. *J. Org. Chem.* **2014,** *80* (1), 438-446.

17. (a) Baar, M. R.; Ballesteros, P.; Roberts, B. W., Interception of [2+2] cycloadducts in the zinc bromide mediated reaction of di-tert-butyl methylenemalonate with simple enol ethers. *Tetrahedron Lett.* **1986,** *27* (19), 2083-2086; (b) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M., From $PtCl_2$- and Acid-Catalyzed to Uncatalyzed Cycloisomerization of 2-Propargyl Anilines: Access to Functionalized Indoles. *Angew. Chem. Int. Ed.* **2007,** *46* (11), 1881-1884; (c) Cera, G.; Piscitelli, S.;

Chiarucci, M.; Fabrizi, G.; Goggiamani, A.; Ramón, R. S.; Nolan, S. P.; Bandini, M., One-Pot Gold-Catalyzed Synthesis of Azepino[1,2-*a*]indoles. *Angew. Chem. Int. Ed.* **2012,** *51* (39), 9891-9895; (d) Gritsch, P. J.; Stempel, E.; Gaich, T., Enantioselective Synthesis of Cyclohepta[*b*]indoles: Gram-Scale Synthesis of (S)-SIRT1-Inhibitor IV. *Org. Lett.* **2013,** *15* (21), 5472-5475; (e) He, S.; Hsung, R. P.; Presser, W. R.; Ma, Z.-X.; Haugen, B. J., An Approach to Cyclohepta[b]indoles through an Allenamide (4 + 3) Cycloaddition–Grignard Cyclization–Chugaev Elimination Sequence. *Org. Lett.* **2014,** *16* (8), 2180-2183; (f) Kusama, H.; Suzuki, Y.; Takaya, J.; Iwasawa, N., Intermolecular 1,5-Dipolar Cycloaddition Reaction of Tungsten-Containing Vinylazomethine Ylides Leading to Seven-Membered Heterocycles. *Org. Lett.* **2006,** *8* (5), 895-897; (g) Mei, G.; Yuan, H.; Gu, Y.; Chen, W.; Chung, L. W.; Li, C.-c., Dearomative Indole [5+2] Cycloaddition Reactions: Stereoselective Synthesis of Highly Functionalized Cyclohepta[*b*]indoles. *Angew. Chem. Int. Ed.* **2014,** *53* (41), 11051-11055.

18. (a) Cavitt, M. A.; Phun, L. H.; France, S., Intramolecular donor-acceptor cyclopropane ring-opening cyclizations. *Chem. Soc. Rev.* **2014,** *43* (3), 804-818; (b) Aponte-Guzmán, J.; Taylor, J. E.; Tillman, E.; France, S., Catalytic, Formal Homo-Nazarov-Type Cyclizations of Alkylidene Cyclopropane-1,1-Ketoesters: Access to Functionalized Arenes and Heteroaromatics. *Org. Lett.* **2014,** *16* (14), 3788-3791; (c) Patil, D. V.; Cavitt, M. A.; France, S., Diastereoselective Synthesis of (±)-Deethyleburnamonine Using A Catalytic Cyclopropane Ring-Opening/Friedel-Crafts Alyation Strategy (Dedicated to Dr. Albert Padwa on his 75th birthday). *Heterocycles* **2012,** *84* (2), 1363-1373; (d) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S., An efficient synthesis of hydropyrido[1,2-*a*]indole-6(7H)-ones via an In(III)-catalyzed tandem cyclopropane ring-opening/Friedel-Crafts alkylation sequence. *Chem. Commun.* **2011,** *47* (37), 10278-10280; (e) Patil, D. V.; Phun, L. H.; France, S., Indium-Catalyzed Homo-Nazarov Cyclizations of Alkenyl Cyclopropyl Ketones. *Org. Lett.* **2010,** *12* (24), 5684-5687; (f) Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S., A Catalytic Homo-

Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones. *Org. Lett.* **2011,** *13* (8), 1952-1955; (g) Shenje, R.; Williams, C. W.; Francois, K. M.; France, S., Catalysis and Chemodivergence in the Interrupted, Formal Homo-Nazarov Cyclization Using Allylsilanes. *Org. Lett.* **2014,** *16* (24), 6468-6471.

19. (a) Corey, E. J.; Balanson, R. D., A simple synthesis of (±)-cedrene and (±)-cedrol using a synchronous double annulation process. *Tetrahedron Lett.* **1973,** *14* (34), 3153-3156; (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M., Total Synthesis of Prostaglandins F2α and E2 as the Naturally Occuring Forms. *J. Am. Chem. Soc.* **1970,** *92* (2), 397-398; (c) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J., Catalytic Formal Homo-Nazarov Cyclization. *Org. Lett.* **2009,** *11* (4), 1023-1026; (d) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J., Formal Homo-Nazarov and Other Cyclization Reactions of Activated Cyclopropanes. *Chem. Eur. J.* **2011,** *17* (51), 14527-14538; (e) Lifchits, O.; Charette, A. B., A Mild Procedure for the Lewis Acid-Catalyzed Ring-Opening of Activated Cyclopropanes with Amine Nucleophiles. *Org. Lett.* **2008,** *10* (13), 2809-2812; (f) Marino, J. P.; Long, J. K., New strategies for annulations: a highly convergent and stereoselective synthesis of an octahydronaphthalene synthon for dihydrocompactin. *J. Am. Chem. Soc.* **1988,** *110* (23), 7916-7917; (g) Murphy, W. S.; Wattanasin, S., A new cyclisation involving cyclopropyl ketones. A short route to 1-aryltetralones. *Tetrahedron Lett.* **1980,** *21* (19), 1887-1890; (h) Pohlhaus, P. D.; Johnson, J. S., Enantiospecific Sn (II)-and Sn (IV)-catalyzed cycloadditions of aldehydes and donor-acceptor cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (46), 16014-16015; (i) Pohlhaus, P. D.; Johnson, J. S., Enantiospecific Sn(II)- and Sn(IV)-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (46), 16014-16015; (j) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S., Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate Ion Pair Pathway. *J. Am. Chem. Soc.* **2008,** *130* (27), 8642-8650;

(k) Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y., Highly Diastereoselective Construction of Fused Carbocycles from Cyclopropane-1,1-dicarboxylates and Cyclic Enol Silyl Ethers: Scope, Mechanism, and Origin of Diastereoselectivity. *Chem. Eur. J.* **2012,** *18* (8), 2196-2201; (l) Reissig, H.-U.; Zimmer, R., Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003,** *103* (4), 1151-1196; (m) Schneider, T. F.; Kaschel, J.; Werz, D. B., A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2014,** *53* (22), 5504-5523; (n) Schneider, T. F.; Werz, D. B., Ring-Enlargement Reactions of Donor−Acceptor-Substituted Cyclopropanes: Which Combinations are Most Efficient? *Org. Lett.* **2011,** *13* (7), 1848-1851; (o) Stork, G.; Marx, M., Six-membered rings via olefin participation in the opening of acylcyclopropanes. *J. Am. Chem. Soc.* **1969,** *91* (9), 2371-2373; (p) Wales, S. M.; Walker, M. M.; Johnson, J. S., Asymmetric Synthesis of Indole Homo-Michael Adducts via Dynamic Kinetic Friedel–Crafts Alkylation with Cyclopropanes. *Org. Lett.* **2013,** *15* (10), 2558-2561; (q) Yu, M.; Pagenkopf, B. L., Formal [3 + 2] Cycloadditions of Donor−Acceptor Cyclopropanes and Nitriles. *J. Am. Chem. Soc.* **2003,** *125* (27), 8122-8123.

20. (a) Brimioulle, R.; Bach, T., [2+2] Photocycloaddition of 3-Alkenyloxy-2-cycloalkenones: Enantioselective Lewis Acid Catalysis and Ring Expansion. *Angew. Chem. Int. Ed.* **2014,** *53* (47), 12921-12924; (b) de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J., Cyclization and annulation reactions of nitrogen-substituted cyclopropanes and cyclobutanes. *Chem. Commun.* **2014,** *50* (75), 10912-10928; (c) Machin Ben, P., $BF_3{\cdot}OEt_2$-catalyzed reaction of donor-acceptor cyclobutanes with terminal alkynes: single-step access to 2,3-dihydrooxepines. *Synlett* (19), 2799-2802; (d) Matsuo, J.-i., 1,4-Zwitterionic intermediates formed by cleavage of a cyclobutane ring and their cycloaddition reactions. *Tetrahedron Lett.* **2014,** *55* (16), 2589-2595; (e) Parsons, A. T.; Johnson, J. S., Formal [4 + 2] Cycloaddition of Donor−Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted

Tetrahydropyrans. *J. Am. Chem. Soc.* **2009,** *131* (40), 14202-14203; (f) Stevens, A. C.; Palmer, C.; Pagenkopf, B. L., The Formal [4+3] Cycloaddition between Donor−Acceptor Cyclobutanes and Nitrones. *Org. Lett.* **2011,** *13* (6), 1528-1531; (g) Vemula, N.; Stevens, A. C.; Schon, T. B.; Pagenkopf, B. L., The [4+2] cycloaddition of donor-acceptor cyclobutanes and nitrosoarenes. *Chem. Commun.* **2014,** *50* (14), 1668-1670.

21. Byrne, L. A.; Gilheany, D. G., Simple syntheses of seven-membered rings via an entropy/strain reduction strategy. *Synlett* **2004,** (6), 933-943.

22. (a) Ballini, R.; Palmieri, A.; Petrini, M.; Torregiani, E., Solventless Clay-Promoted Friedel−Crafts Reaction of Indoles with α-Amido Sulfones: Unexpected Synthesis of 3-(1-Arylsulfonylalkyl) Indoles. *Org. Lett.* **2006,** *8* (18), 4093-4096; (b) Jiang, R.; Wu, X.-J.; Zhu, X.; Xu, X.-P.; Ji, S.-J., Ferric(III) Nitrate: An Efficient Catalyst for the Regioselective Friedel–Crafts Reactions of Indoles and tert-Enamides in Water. *Eur. J. Org. Chem.* **2010,** *2010* (31), 5946-5950; (c) Zhou, J.; Tang, Y., Enantioselective Friedel-Crafts reaction of indoles with arylidene malonates catalyzed by iPr-bisoxazoline-Cu(OTf)$_2$. *Chem. Commun.* **2004,** (4), 432-433; (d) Jorgensen, K. A., Asymmetric Friedel-Crafts reactions: catalytic enantioselective addition of aromatic and heteroaromatic CH bonds to activated alkenes, carbonyl compounds, and imines. *Synthesis* **2003,** (7), 1117-1125.

23. (a) Lee-Ruff, E., Synthesis of Cyclobutanes. In *The Chemistry of Cyclobutanes*, John Wiley & Sons, Ltd: **2005**; pp 281-355; (b) Rappoport, Z.; Liebman, J. F., *The chemistry of cyclobutanes*. John Wiley & Sons: **2005**.

24. (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B., Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003,** *103* (4), 977-1050; (b) Charette, A. B.; Beauchemin, A., Simmons-Smith Cyclopropanation Reaction. In *Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

25. Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Pérez-Fernández, M., Selective Michael−Aldol Reaction by Use of Sterically Hindered Aluminum Aryloxides

as Lewis Acids: An Easy Approach to Cyclobutane Amino Acids. *Org. Lett.* **2005,** *7* (16), 3597-3600.

26. (a) Amir Siadati, S., Effect of steric congestion on the stepwise character and synchronicity of a 1, 3-dipolar reaction of a nitrile ylide and an olefin. *J. Chem. Res.* **2015,** *39* (11), 640-644; (b) Darù, A.; Roca-López, D.; Tejero, T.; Merino, P., Revealing Stepwise Mechanisms in Dipolar Cycloaddition Reactions: Computational Study of the Reaction between Nitrones and Isocyanates. *J. Org. Chem.* **2016,** *81* (2), 673-680; (c) Domingo, L. R.; Arnó, M.; Contreras, R.; Pérez, P., Density Functional Theory Study for the Cycloaddition of 1,3-Butadienes with Dimethyl Acetylenedicarboxylate. Polar Stepwise vs Concerted Mechanisms. *J. Phys. Chem. A* **2002,** *106* (6), 952-961; (d) Hoffmann, R.; Woodward, R. B., Selection Rules for Concerted Cycloaddition Reactions. *J. Am. Chem. Soc.* **1965,** *87* (9), 2046-2048; (e) Siadati, S. A., A Theoretical Study on Stepwise-and Concertedness of The Mechanism of 1, 3-Dipolar Cycloaddition Reaction between Tetra Amino Ethylene and Trifluoro Methyl Azide. *Comb. Chem. High Throughput Screen.* **2016,** 19 (2), 170-175; (f) Ylijoki, K. E. O.; Stryker, J. M., [5 + 2] Cycloaddition Reactions in Organic and Natural Product Synthesis. *Chem. Rev.* **2013,** *113* (3), 2244-2266.

27. McPhail, A. T.; Onan, K. D., Crystal and molecular structure of carolenalone, a cycloheptenone sesquiterpene lactone from North Carolina Helenium autumnale L. *J. Chem. Soc., Perkin Trans. 2* **1976,** (3), 332-335.

28. Davies, J.; Leonori, D., The first calcium-catalysed Nazarov cyclisation. *Chem. Commun.* **2014,** *50* (96), 15171-15174.

29. Matziari, M.; Nasopoulou, M.; Yiotakis, A., Active Methylene Phosphinic Peptides: A New Diversification Approach. *Org. Lett.* **2006,** *8* (11), 2317-2319.

30. Fryszkowska, A.; Fisher, K.; Gardiner, J. M.; Stephens, G. M., Highly Enantioselective Reduction of β,β-Disubstituted Aromatic Nitroalkenes Catalyzed by Clostridium sporogenes. *J. Org. Chem.* **2008,** *73* (11), 4295-4298.

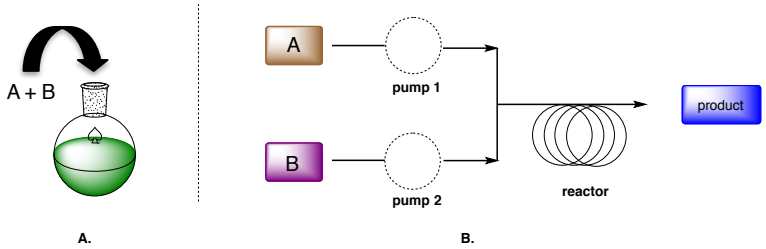
31. Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M., Hydrazines and Azides via the Metal-Catalyzed Hydrohydrazination and Hydroazidation of Olefins. *J. Am. Chem. Soc.* **2006,** *128* (35), 11693-11712.

CHAPTER 4 CONTINUOUS FLOW TANDEM CYCLOPROPANATION/RING-OPENING CYCLIZATIONS[††,1]

4.1 Introduction

Since the birth of synthetic chemistry, chemists have used batch set-ups to undertake organic reactions. These traditional batch-wise processes feature a single reaction vessel in which reactants, reagents and solvents are mixed to effect a specific transformation (Scheme 4.1, A). Upon completion of the desired reaction, reactor contents then typically undergo workup then purification protocols to produce final compounds. In contrast, continuous flow setups feature a steady stream of solvent containing reactants and reagents that are fed into a reactor via a series of pumps (Scheme 4.1, B). Under this regime, starting materials react as they traverse the reactor coil. While continuous flow technology has been utilized extensively by chemical engineers for more than a century, its miniaturization and adoption by synthetic chemists is a recent phenomenon. Much of the application of continuous flow in the engineering sector involves very large-scale applications; chemists have now scaled down this technology and applied it to towards undertaking sustainable organic chemistry transformations.[2]

[††] Work on the continuous flow synthesis of hydropyrido[1,2-*a*]indoles performed in collaboration with Joel Aponte-Guzman and the Liotta-Eckert Lab at GA Tech. Published in *Ind. Eng. Chem. Res.* **2015**, *54*, 9550.



Scheme 4.1. Batch and Continuous Flow Reaction Set-ups.

4.2 Batch vs Continuous Flow

Being from very distinct operational regimes, batch and continuous flow reactions are governed by different principles. For example, in the batch regime, reaction time simply refers to the amount of time elapsed between addition of reagents and quenching of reaction mixture. In continuous flow, reaction time is governed by residence time, t_R, which is the length of time a solution resides in the reactor. Residence time is a function of flow rate and reactor volume. Very fast reactions need only spend minimal time in the reactor and therefore can be effectuated using high flow rate, and vice versa.[3]

Reaction stoichiometry is another property that is visualized differently in batch as opposed to continuous flow regimes. Concentration of reagents and their volumetric ratios govern stoichiometry under batch conditions whereas reagent concentration and ratios of their flow rates apply to continuous flow. In a flow reactor, the flow rates of the different reagent inlets need not be the same; application of a stoichiometric or super-stoichiometric amount of a single reagent can undertaken by increasing it flow rate and/or concentration independent of the other reagent inlets.[4]

Whether a reaction is being performed under batch or flow conditions, it is crucial that reagents be mixed efficiently for optimal control of reaction kinetics and, ultimately, chemical yields. Mixing under batch conditions involves use of impellers, whose rotation

induces mechanical agitation of the fluidic system. Under these conditions, referred to as macromixing, the mixing is directly dependent on type of impeller employed and rate of stirring and involves a chaotic combination of laminar, turbulent and transitional patterns of flow. Flow reactors operate in two different paradigms of mixing: micromixing and macromixing. Micromixing is the dominant paradigm microreactor systems; herein laminar flow is experienced (Reynolds number, Re < 1) and mixing is governed by diffusion rates between fluids involved. Micromixing can be spectacularly efficient; complete mixing can be achieved in a fraction of a second. Macromixing for larger scale flow reactor can be laminar, turbulent and transitional patterns of flow depending on Re; most laboratory-type flow reactor involved laminar and transitional flow. For both micro- and macromixing paradigms in flow reactors, additional strategies, such as mixing beds, can be employed to improve the rate and extent of mixing of fluid/reagents.[5] Ultimately, these mixing strategies for flow chemistry significantly more effective mass transport compared to batch configurations.

In synthetic chemistry, it is often critical that a transformation be performed at a certain, specific temperature. Carrying out reactions under known, isothermal conditions allows better mapping and prediction of reaction kinetics; this, in turn, enables more precision and reproducibility. At large reaction scales in industry, precision and reproducibility of reactions are of the utmost importance as they directly correlate to efficiency and cost of the overall chemical processes. In addition, highly exothermic transformations need efficient heat transfer to prevent self-propagative, runaway chain reactions while endothermic reactions, if unchecked, can lead to self-quenching and stalling. It is therefore imperative that heat transfer for reactions (both exothermic and

endothermic) be as efficient as possible. Under batch conditions, the mechanism of heat transfer depends convective factors wherein vigorous stirring creates convection currents that transfer heat to the reactor walls. For flow systems, however, heat transfer is predominantly a factor of thermal conduction through the fluid itself. As a result, reactor thickness is an important parameter for rate/efficiency of heat transfer; thinner reactor diameters intrinsically have larger surface area-to-volume ratio and therefore can conduct heat more effectively. Reactor material also plays a crucial role in heat transfer for flow systems. Generally, thinner reactors as well as high conductivity reactor materials offer superior heat transfer to and fro the reaction medium.[5a]

Another important distinction between batch and flow reactors configurations pertains to reaction scale-up. In batch, scale-ups are a function of vessel size; large reactions are performed using proportionately large reaction vessels capable of supporting large amounts of material. Industrial scale batch reactors can be immense, occupying an enormous footprint. In contrast, reaction scale-ups for flow reactions can be effectuated by adjustments in flow rate, reactor volume, and reactor runtime. High flow rates and large reactor volumes lead to higher throughput with marginal increases in footprint in many cases. In addition, maintaining a constant flow rate and reactor volume while allowing longer runtimes also achieves increases in total reaction output even though the intrinsic reactor throughput remains unchanged. Finally, flow reactors offer the option of "scaling-out" reactions as opposed to "scaling-up". Scaling-out involves setting up multiple, parallel flow reactor modules that may or may not utilize the same starting material reservoirs. This allows large product output without the need to recalculate or re-engineer reactor dimensions, flow rates and heating/cooling protocols.[6]

There are many advantages of continuous flow reactors (CFRs) over batch reactors (BRs) for synthetic chemistry applications. Since the reactor thicknesses and volume are relatively small, temperature control and mixing of reagents are much more efficient in CFRs compared to BRs. Additionally, the efficient temperature control and mixing in CFRs allows certain reactions to even be carried out under solvent-free conditions which reduces the amount of waste generated in a synthetic transformation. Another advantage of CFRs is that they can be more easily automated compared to BRs. Devices such as auto-samplers and in-line detectors can be connected to the CFR system such that preliminary data analysis can be performed automatically. Furthermore, workups and purifications can be paired to a flow reactor using strategies such as solid phase scavenging, liquid/liquid extraction, and chromatography. On the other hand, automation of BRs is non-trivial.

By maintaining relatively small reactions volumes, CFRs are generally considered a safer vehicle for handling highly hazardous reagents or undertaking transformations whose exothermicity can potentially lead to dangerous runaway reactions. Other important benefits of continuous flow include: (1) ease of scale-up or scale-out using a small footprint; (2) the ability to heat reactors above the solvents' boiling points; (3) lowered production costs; (4) increased reaction reproducibility and enhanced product quality; and (5) the potential for uninterrupted, multi-step reaction sequences.[3, 5a]

Notably, while it offers numerous benefits over batch as a vehicle for synthetic chemistry, continuous flow does have a few drawbacks: (1) initial costly capital investment for pumps, reactors, and peripheral devices; and (2) incompatibility with reactions whose products precipitate out of solution.[7] Despite these challenges, flow

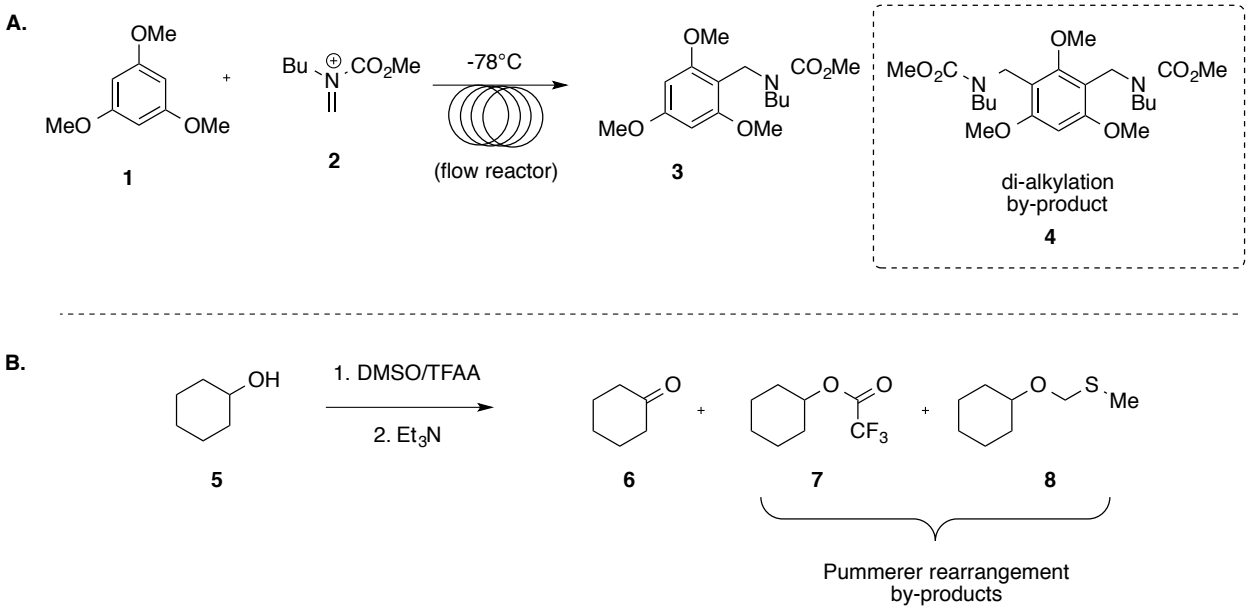
reactor systems are an indispensible enabling technology for undertaking synthetic chemistry, and therefore are consequently gaining popularity in the synthetic community as viable alternative reaction vehicles. Many exciting research areas involving flow chemistry are currently being explored and include: (1) coupling flow reactors with microwave technology;[6] (2) application of flow systems to highly reactive/sensitive intermediates;[3] (3) supported reagents/catalysts for heterogeneous reactivity;[8] (4) multicomponent and multistep transformations;[9] and (5) coupling of flow and photochemistry.[10] Much success has already been achieved in these areas, making continuous flow reactions a key and unparalleled strategy for the future.

4.3 Recent applications of flow technology

There are a number of transformations whose reaction timescales are so short (at cryogenic or ambient temperatures) that the rate of mixing becomes particularly important. For these reactions, it is crucial that the timescale for mixing be greater than that of the actual reaction itself in order to reduce local "pockets" of intermediates or product where the localized concentration can lead to side reactivity, producing by-products. Micron-sized flow reactors enable rapid micromixing allowing mixing rates faster than would be possible with mechanical agitation under batch set-ups.[5a]

The Friedel-Crafts-type aminoalkylation of trimethoxybenzene **1** with iminium **2** is one example that benefits microflow reactivity (Scheme 4.2, A).[11] Under batch conditions, this transformation proved highly inefficient and only a 36% yield of desired product **3** was obtained. This low yield was due to formation of the di-alkylated by-product **4**. In contrast, fast micromixing afford by flow chemistry enabled suppression of

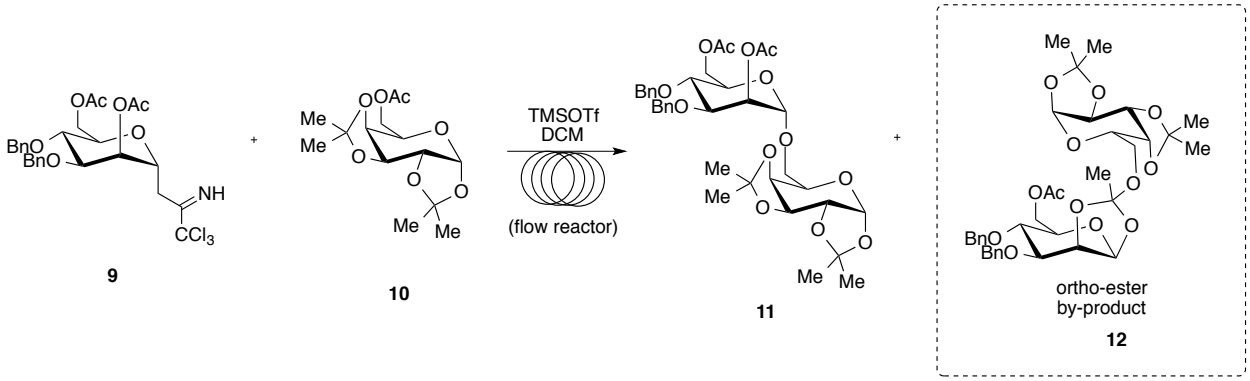
this competitive dialkylation leading to a 92% isolated yield of **3**. In another example, a Moffatt-Swern-type oxidation of alcohol **5** to ketone **6** proved particularly indicative of the superiority of flow reactors over batch systems (Scheme 4.2, B).[12] The transformation was difficult to perform under batch reaction conditions (-20 °C) due to formation of the Pummerer rearrangement by-products **7** and **8**. Continuous flow allowed fast micromixing to produce desired ketone **6** in 88% yield in 10 ms at 20 °C.[5a, 13]



Scheme 4.2. Continuous Flow Friedel-Crafts Alkylation.

As testament to its utility towards synthesis of natural products, microreactor-based methodology optimization was performed in an important glycosylation transformation (Scheme 4.3). The benefit of flow chemistry in this case was its ability to be integrated with reaction-monitoring technology such as UV-Vis and LC-MS. Under this efficient configuration, reactions temperatures were easily varied across -78 °C to -20 °C temperature range in addition to utilization of flow rates varying from 10-80 μL/min.

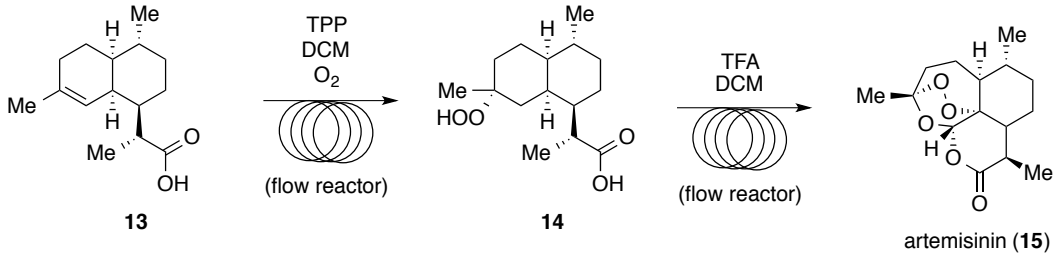
Taking in account all these variables, it was established that the formation of desired product **11** was directly related to temperature, and reaction time/flow rate. The undesired ortho ester **12** tended to be formed at -70 °C in with reaction times on the order or 60 s whereas the optimal condition for formation of the desired product **11** was observed between -60 °C and -40 °C in reaction timescales of about 210 s. While such precise monitoring of this fast reactivity was easily performed using a multi-variable flow strategy, its corresponding batch optimizations would have been extremely challenging.[5a, 14]



Scheme 4.3. Continuous Flow Glycosylation.

Artemisinin **15** is an interesting sesquiterpene possessing unparalleled bioactivity for the treatment of multi-drug resistant malaria strains.[15] Typical sources for this molecule for commercial use involve its direct isolation from the *Artemisia annua* plant or total synthesis via synthetic routes impractical on large scales. Methods for practical and cost-effective large-scale synthesis of artemisinin **15** would be of immense benefit to both the synthetic and pharmaceutical communities. A continuous flow semisynthesis of artemisinin **15** via dihydroartemisinic acid **13**, recently developed by Seebeger and co-workers, represents marked success towards that goal (Scheme 4.4).[16] This semisynthesis

involved the singlet oxygen ($^1O_2$) photooxidation of acid **13** to produce peroxide **14**. Singlet oxygen chemistry is highly sensitive and extremely dangerous, two features for which continuous flow technology warrants itself useful due to enabling precise control of mixing, temperature, reaction time, and flow rates. Peroxide **14** was immediately subjected to further continuous flow conditions (TFA/O_2) to enable a Hock cleavage which afforded artemisinin **15** in 39% overall yield in 4.5 min. Importantly, this tandem protocol has the potential to be scale-up (or scaled-out) which would significantly lower production cost for this important anti-malarial compound.[15-16] Many other ingenious continuous flow protocols have carried out for syntheses of a range of interesting natural products such a yessotoxin, (-)-hennoxazole A, spirodienal A, puaciflorol F, vitamin D_3, and aplysamine among others.[15]



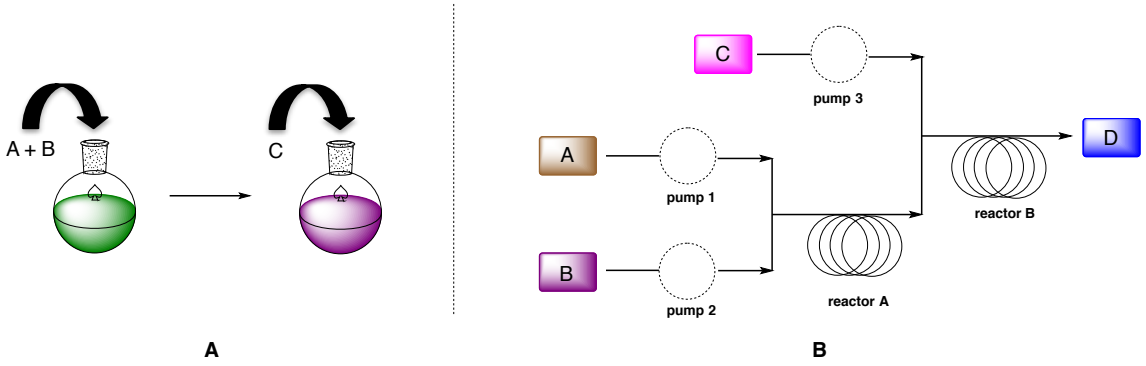
Scheme 4.4. Continuous Flow Synthesis of Artemisinin.

4.4 Multistep Continuous Flow Synthesis

Perhaps the most significant advantage of CFRs over BRs is the ability to undertake uninterrupted multistep syntheses without intermediary purification and isolation. Traditional multistep syntheses under batch conditions involves a linear sequence of reaction operations in which products from preceding steps undergo work-ups, and purifications before being subjected to the next step (Scheme 4.5, A). This process is generally time-consuming, arduous, costly, and leads to waste-generation.

Under multistep continuous flow conditions, processes are streamlined such that products of earlier transformations are fed directly into subsequent steps (Scheme 4.5, B).

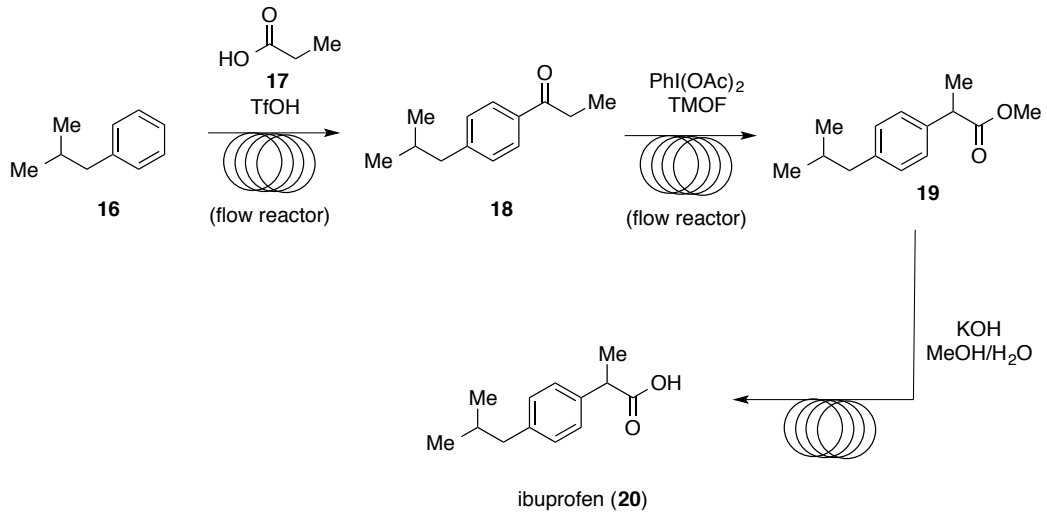
Many considerations have to be taken into account for successful implementation of multistep continuous flow synthesis: (1) by-products of earlier steps must interfere with downstream steps; otherwise they should be removed (using inline strategies such immobilized reagents or scavengers); (2) processes must be sequenced so as to ensure solvent compatibility; (3) flow rates, and reactant concentrations must be well-managed at each stage; (4) engineering aspects must be taken into account for optimal choice of reactor type, dimensions, and heating/cooling mechanisms.[8-9]



Scheme 4.5. Batch and Continuous Flow Multi-Step Set-ups.

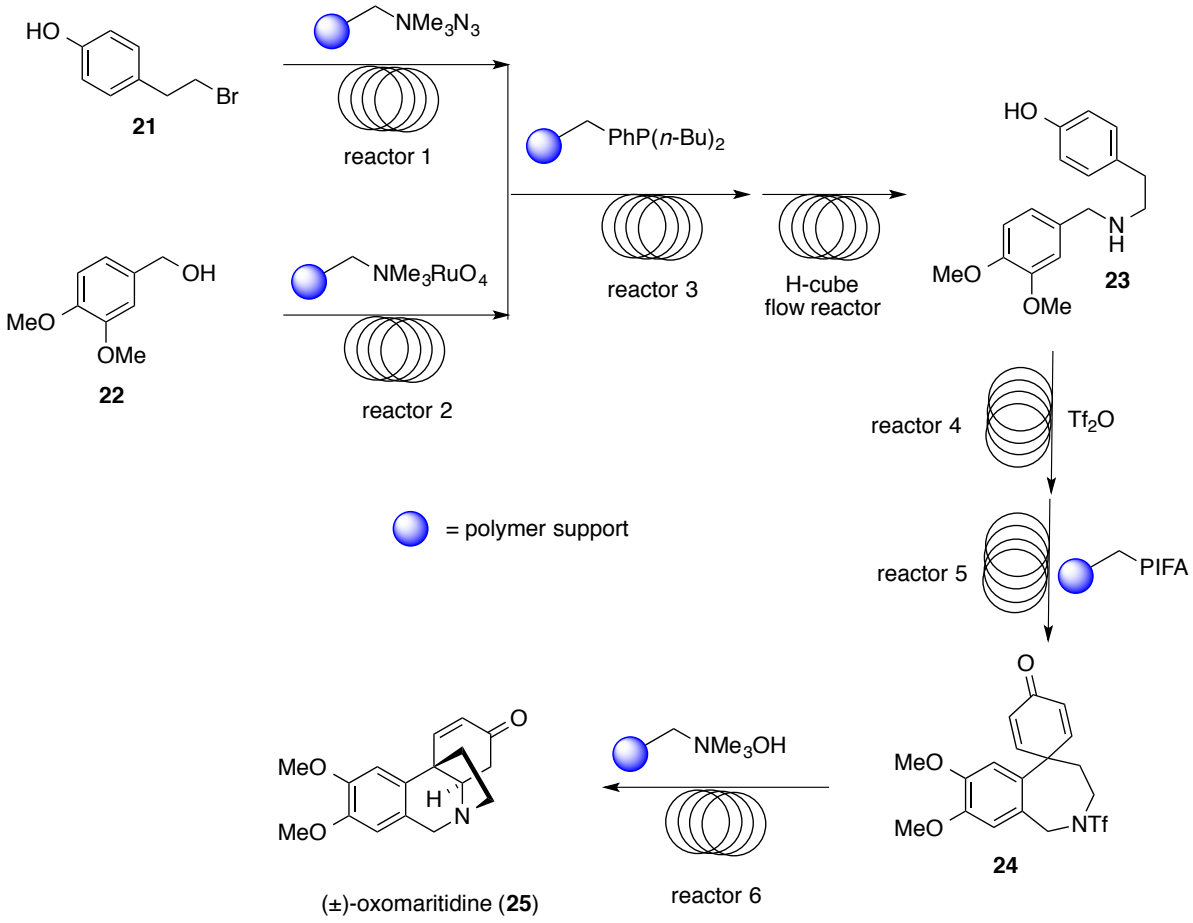
In an effort to leverage the benefits of multistep continuous flow synthesis, McQuade and co-workers applied it to the synthesis of ibuprofen (Scheme 4.6).[17] In the first step, neat streams of isobutylbenzene **16** and propionic acid **17** were fed into reactor 1 wherein a Friedel-Crafts transformation afforded ketone **18**. This ketone was then fed, directly, into the next flow reactor where trimethyl orthoformate and iodosobenzene acetate induced a 1,2-aryl migration that led to ester **19**. Finally, a saponification using KOH afforded the desired ibuprofen **20** through either chromatographic purification (70%) or recrystallization (51%). This three-step continuous flow synthesis enabled an

efficient and streamlined synthesis of ibuprofen **20** without an intermediary workups or purification.



Scheme 4.6. Continuous Flow Synthesis of Ibuprofen.

In an elegant attempt to showcase the utility of continuous towards accessing natural products, Ley and co-workers reported a six-step flow sequence to the indole alkaloid (±)-oxomaritidine (**25**) (Scheme 4.7).[18] All the steps in this sequence were carried out in flow and involve: (1) nucleophilic formation of an azide from bromide **21** (reactor 1); (2) formation of Staudinger phosphinimine and an aza-Wittig reaction (with the aldehyde from reactor 2); (3) the imine from reactor 3 was reduced in an H-Cube to afford amine **23**; (4) *N*-triflation in reactor 4 and a subsequent PIFA-oxidation and coupling (in reactor 5) to yield ketone **24**; (5) deprotection and 1,4-addition led to (±)-oxomaritidine (**25**). Through careful ordering of synthetic steps and the use of polymer-supported in-line reagents, an all-flow sequence enabled the formation of (±)-oxomaritidine (**25**) in an impressive 40% overall yield.



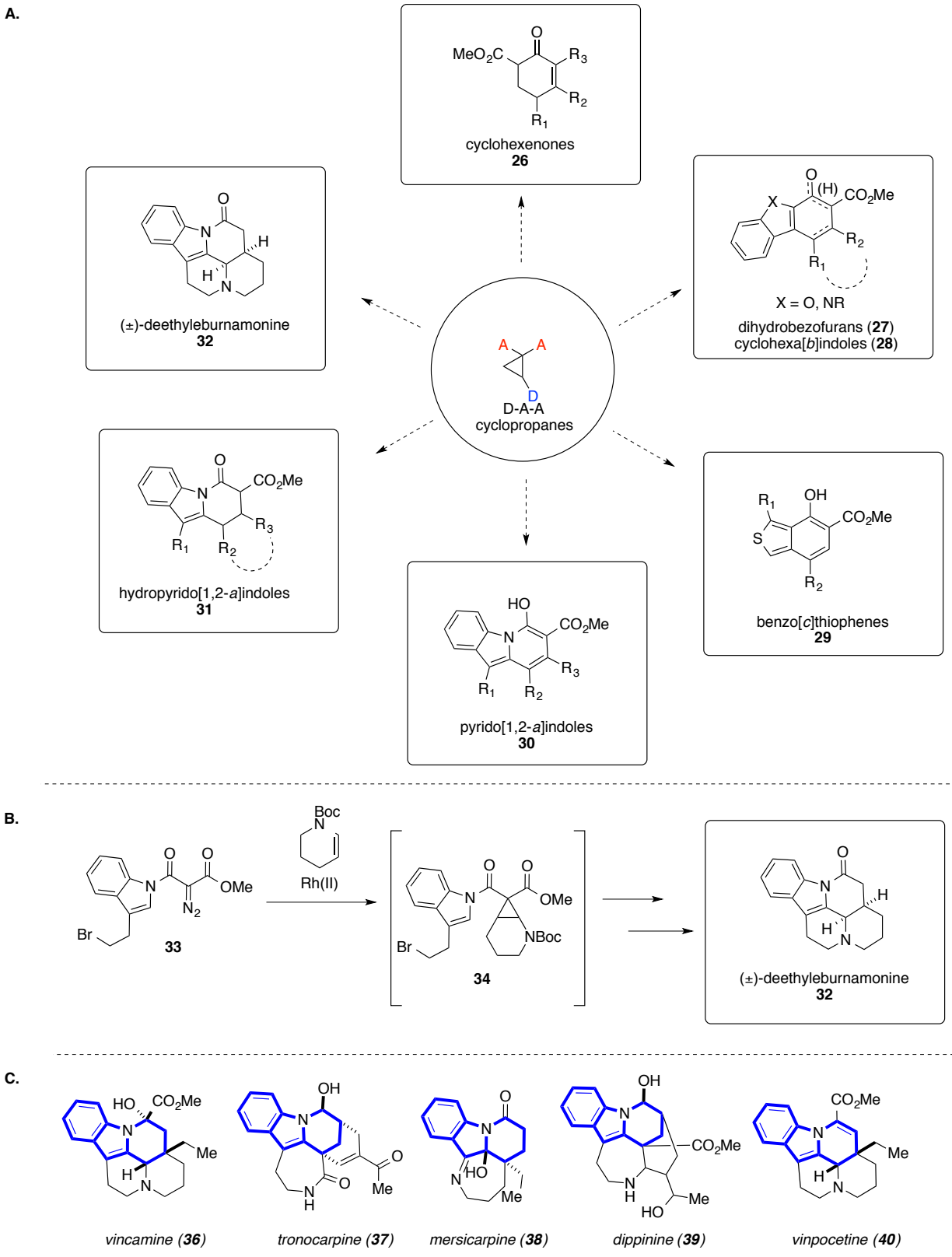
Scheme 4.7. Continuous Flow Synthesis of (±)-Oxomaritidine.

4.5 Development of Tandem Cyclopropanation/Ring-Opening Cyclizations in Flow

4.5.1 Project Rationale and Justification

The France group has continually been interested in developing homo-Nazarov and homo-Nazarov-inspired chemistry for access to interesting molecular scaffolds as well as for the total synthesis of natural products (Scheme 4.8). Successful manipulation of these types of reactions using D-A-A cyclopropane precursors has provided access into chemical scaffolds such as cyclohexenones (**26**), dihydrobenzofurans (**27**), cyclohexa[*b*]indoles (**28**), benzo[*c*]thiophenes (**29**), pyrido[1,2-*a*]indoles (**30**), hydropyrido[1,2-*a*]indoles (**31**), among many other benzo-fused heteroaromatics

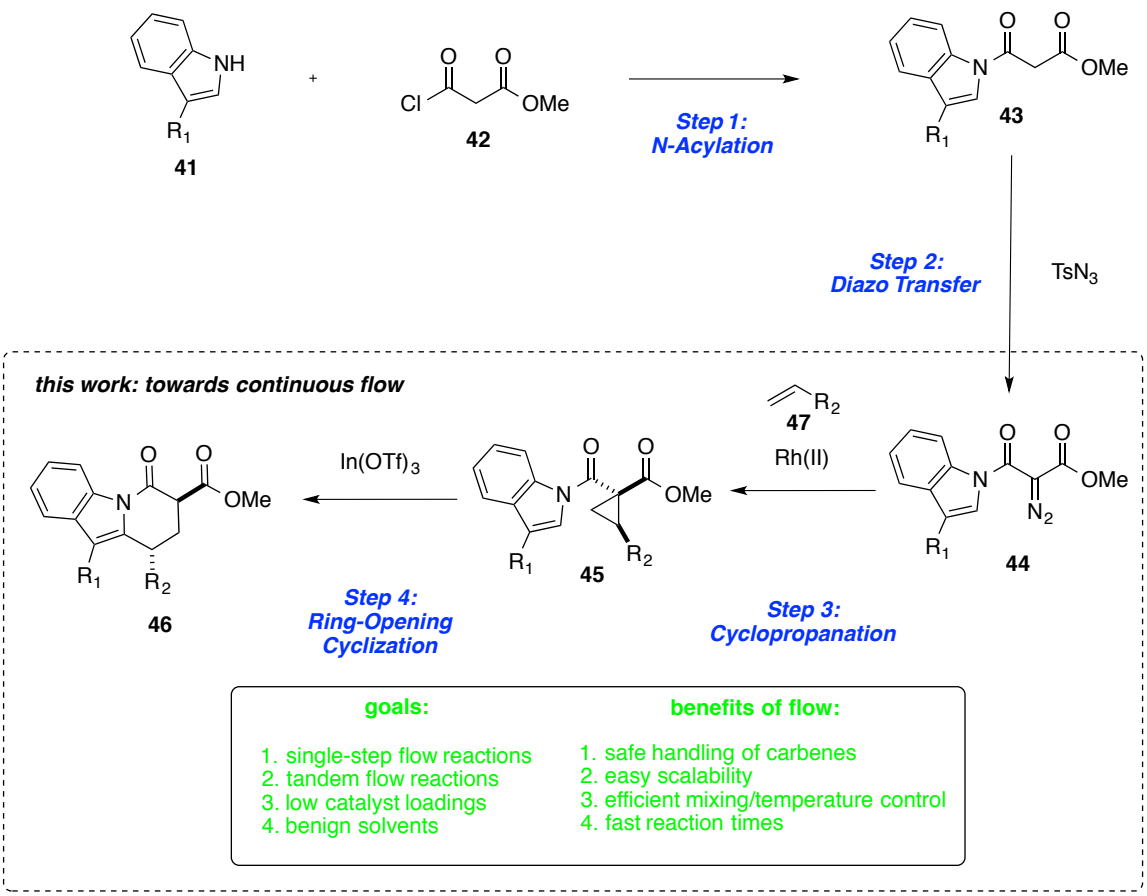
(Scheme 4.8, A).[19] In addition, as testament to the ultimate utility of homo-Nazarov-inspired chemistry, D-A-A cyclopropane **34** was synthesized *en route* to the total synthesis of (±)-deethyleburnamonine (**32**) (Scheme 4.8, B).[19a] Many other alkaloid natural products bearing the hydropyrido[1,2-*a*]indole scaffold exist and have been subject to much synthetic effort (Scheme 4.8, C).[19a, 20] Given the importance of this core, integration of hydropyrido[1,2-*a*]indole synthesis with the benefits of flow chemistry would be of value to the synthetic/industrial community through enabling large-scale production in controlled, streamlined, and sustainable fashion. Furthermore, tandem cyclopropanation/cyclization protocols in flow have yet to be reported in literature; developing a method in this realm would benefit the fields of D-A-A cyclopropane as well as homo-Nazarov-type chemistry.



Scheme 4.8. Importance of Hydropyrido[1,2-*a*]indoles.

4.5.2 Reaction Design

Hydropyrido[1,2-*a*]indoles have previously been synthesized, under batch conditions in the France lab, via a 4-step sequence (Scheme 4.9).[19b] An initial *N*-acylation of indoles **41** using methyl malonyl chloride **42** affords *N*-acylated indoles **43** (Step 1). Subsequent diazo transfer using TsN_3 leads to the formation of diazo species **44** (Step 2). In the presence of a Rh(II) catalyst and alkenes **47**, diazos **44** undergo cyclopropanations that produce D-A-A cyclopropanes **45** (Step 3). Finally, $In(OTf)_3$-catalyzed ring-opening cyclization leads to hydropyrido[1,2-*a*]indoles **46** (Step 4). Conceivably, the two most critical transformations in this sequence (Step 3 – Cyclopropanation and Step 4 – Ring-Opening Cyclization) could separately be carried out using flow chemistry. More interestingly, a tandem cyclopropanation/ring-opening cyclization protocol could be envisaged, and would potentially avoid any intermediary work-up or purification. Such an adaptation would conceivably benefit the hydropyrido[1,2-*a*]indole synthesis methodology in the following ways: (1) safe and easy handling of the highly reactive Rh-carbenes formed in the cyclopropanation step; (2) ease of scalability through scale-up or scaling-out strategies; (3) efficient temperature control and mixing enabling fast reaction times. In addition, a sustainable approach in the integration of flow chemistry with this methodology would render it synthetically more appealing if the following aspects were incorporated: (1) use of relatively low catalyst loadings; (2) utilization of benign, environmentally-acceptable solvents. Clearly, the development of an unprecedented, sustainable continuous flow multistep synthesis of hydropyrido[1,2-*a*]indoles would be a significant milestone for the synthetic community.

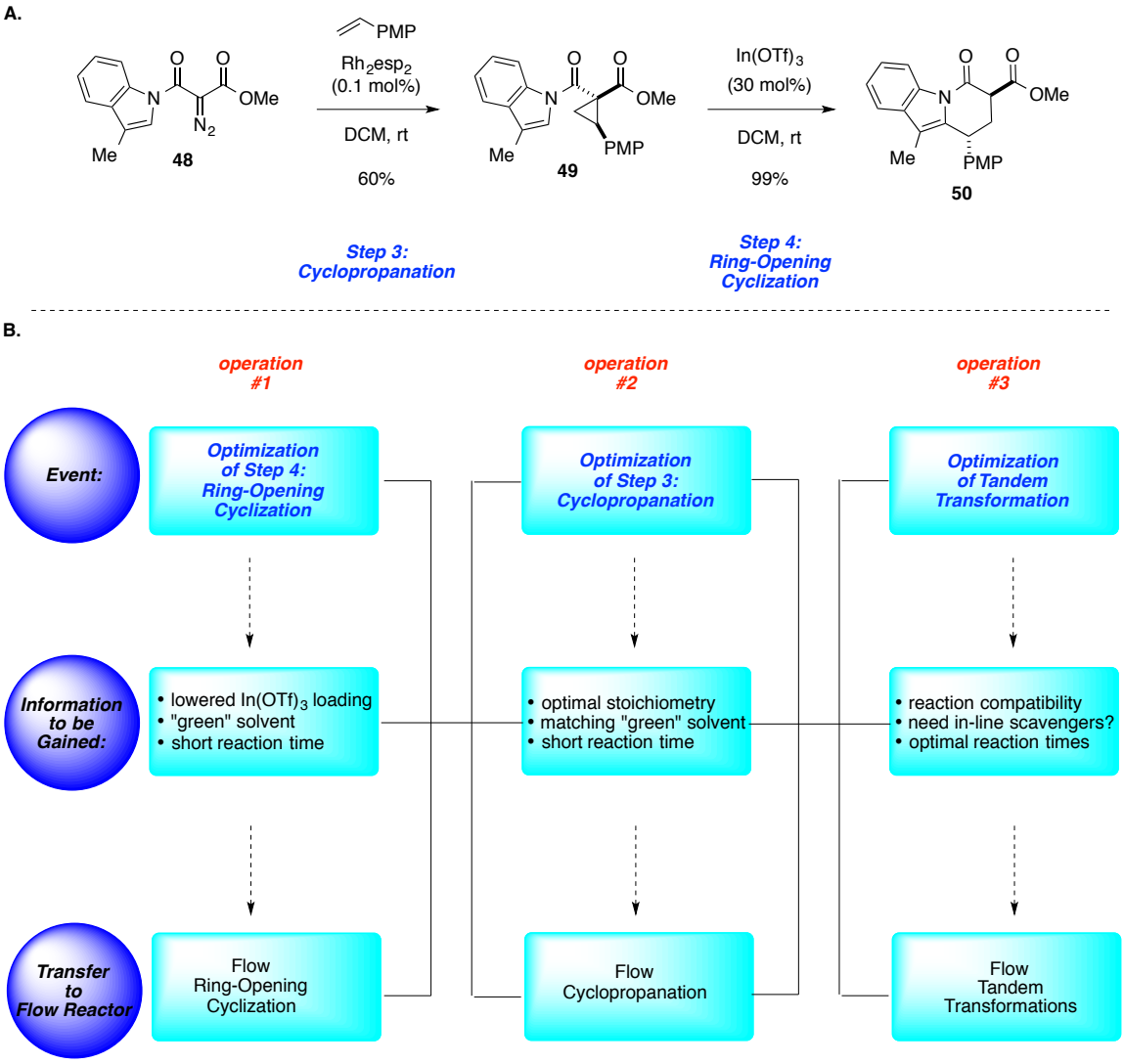


Scheme 4.9. Synthetic Protocol for Hydropyrido[1,2-a]indole Synthesis.

4.5.3 Method Development: Strategy for Transfer from Batch to Flow

The original protocol, developed by France and co-workers under batch conditions, utilized Rh_2esp_2-catalyzed cyclopropanation (60% yield) followed by an $In(OTf)_3$-catalyzed ring-opening cyclization (99% yield) (Scheme 4.10, A).[19b] Both synthetic steps were carried out in DCM, an environmentally unacceptable solvent. In addition, inducing the cycloisomerization of cyclopropane **49** to hydropyridoindole **50** required a 30 mol% $In(OTf)_3$, another undesirable feature of this transformation. Sustainable adoption of this methodology in flow was carried out systematically as shown in Scheme 4.10, B. As a starting point, the more downstream process (step 4 –

ring-opening cyclization) was optimized first followed by the cyclopropanation (step 3). In the first sets of operations, extensive optimization of Step 4 was performed in order to achieve low $In(OTf)_3$ loading, an acceptable "green" solvent, as well as reasonably fast reactivity. After identification of these optimal conditions, their compatibility/applicability in flow was then demonstrated. Next, cyclopropanation was investigated. Here, key learning points were the optimal stoichiometry for this transformation, fast reactivity as well as a solvent identical to that implemented in Step 4. As before, applicability of Rh-cyclopropanation to flow chemistry followed. Finally, given the separate optimized conditions for Step 4 and Step 3, tandem cyclopropanation/cylization transformations were attempted. Several potential complications had to be addressed towards this end: (1) whether or not cyclopropanation and cyclization procedures were indeed compatible to be carried out in a tandem formation; (2) potential interference of any material or by-products from cyclopropanation with the cyclization (which would require in-line scavengers or chromatography); and (3) the ability to maintain the already optimized fast reaction rates for the individual steps. Ultimately, the optimal tandem batch conditions were transferred to continuous flow.



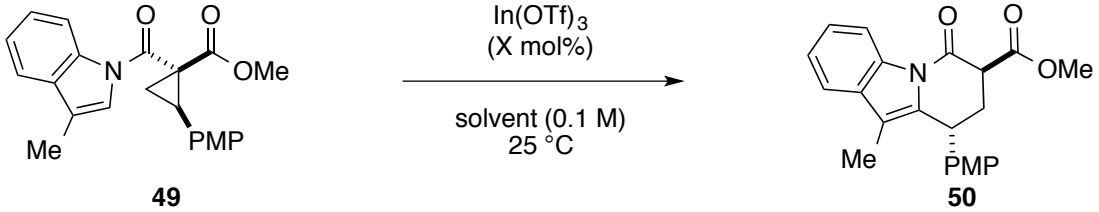
Scheme 4.10. Adoption of Hydropyrido[1,2-*a*]indole Synthesis in Flow.

4.5.3.1 Batch Ring-Opening Cyclization

Cyclopropane **49** was subjected to varying conditions of catalyst loading and solvent, and reaction success was defined as high chemical yields as well as short reaction times (Table **4.1**). Solvents investigated as potential replacements to DCM were chosen in accordance with the Pfizer solvent selection guide.[21] $In(OTf)_3$ was an absolute necessity of the reaction, a reaction without this catalyst did not proceed at all (Table **4.1**, entry 1). In addition, it was generally observed that ethereal solvents gave long reaction

times while alcoholic one completely stalled the reaction (Table **4.1**, entries 3-6). The lack of success using these solvents was attributed to their inability to completely dissolve the cyclopropane starting material **49** and the $In(OTf)_3$ catalyst. As such, these reactions were evidently heterogeneous, a property unsuitable for continuous flow. Additionally, as described in previous chapters, alcoholic solvents also tend to sequester highly oxophilic catalysts, hindering cyclization. On the other hand, solvent such as PhMe, acetone, and MeCN proved worthwhile and led to high reaction conversion in short reaction times (Table **4.1**, entries 8-10). MeCN was particularly promising and was subjected to further optimization (Table **4.1**, entries 10-12). Ultimately, lowering the $In(OTf)_3$ loading to 5 mol% still achieved > 99% conversion in 15 min; these conditions were selected as optimal for batch ring-opening cyclizations (Table **4.1**, entry 12).

Table 4.1. Solvent Screen for Ring-Opening Cyclization[a].



49 **50**

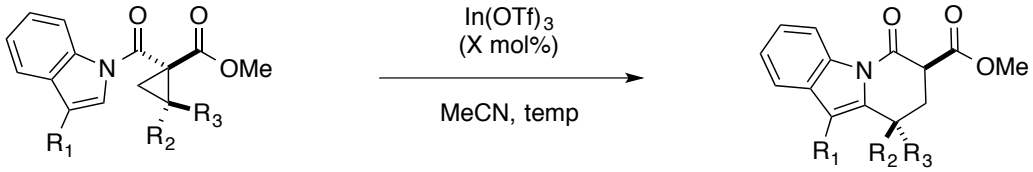
entry	catalyst (mol%)	solvent	time [b]
1	no cat.	DCM	-- [c]
2	30	DCM	15 min
3	30	THF	12 h
4	30	MTBE	9 h
5	30	MeOH	-- [c]
6	30	*i*-PrOH	-- [c]
7	30	PhMe	15 min
8	30	Acetone	30 min
9	30	EtOAc	25 min
10	30	MeCN	15 min
11	10	MeCN	15 min
12	5	MeCN	15 min [d]

[a] Reaction run with **49** (0.3 mmol scale, 1 equiv) and $In(OTf)_3$ (X mol%) in DCM (0.1 M). [b] Time taken to reach > 99% conversion as determined by ^{1}H-NMR. [c] Reaction did not go to completion. d An isolated yield of 96% after column chromatography

The optimized batch conditions (5 mol% $In(OTf)_3$, 0.1 M MeCN, rt)were applied to a set of other cyclopropanes (Table **4.1**). Cyclopropanes **5** and **6** both gave good conversions and yields (90% and 79% respectively) in the 15 min timeframe (Table **4.2**, entries 5-6). However, cyclopropane **49b**, bearing the less activating Me-Ph donor groups, underwent slow reactivity under the optimized conditions as well as with higher catalyst loadings at room temperature (Table **4.2**, entries 1-3). Gratifyingly, increasing

reaction temperature to 50ºC benefited this transformation, and a 99% yield of hydropyridoindole **50** was obtained (Table **4.2**, entries 4).

Table 4.2. Ring-Opening Cyclizations for Other Cyclopropanes[a].



49b (R_1, R_2 = Me; R_3 = Ph
49c (R_1 = CH_2CO_2Me; R_2 = H; R_3 = PMP
49d (R_1 = Me; R_2 = H; R_3 = 2-furyl

entry	**cylopropane #**	catalyst loading (mol%)	temperature (°C)	time	yield (%)
1	**49b**	5	23	24 h	-- [b]
2	**49b**	30	23	24 h	-- (44) [b,c]
3	**49b**	15	23	24 h	94(34) [c,d]
4	**49b**	15	50	10	> 99 [e]
5	**49c**	5	23	10	90 [e]
6	**49d**	5	23	15	79 [e]

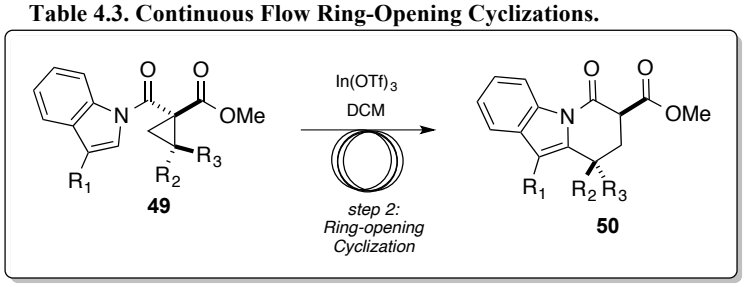
[a] Reaction run with **49** (0.3 - 0.75 mmol scale, 1 equiv) and $In(OTf)_3$ (X mol%) in DCM (0.1 M). [b] Reaction was too slow as determined by ^{1}H-NMR. [c] Yield in parantheses is for prematurate quenching/isolation after 20 min. [d] Yield not in paranthesis was after reaction time of 24 h. [e] Isolated yield after column chromatography.

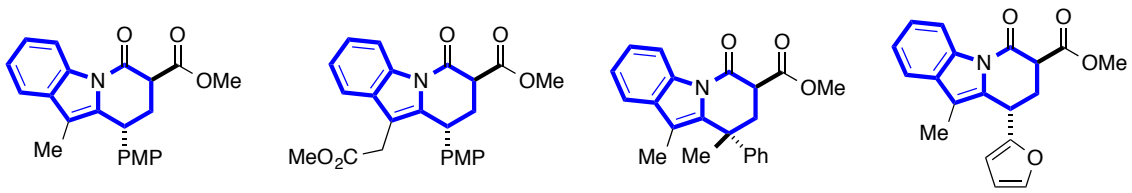
4.5.3.2 Continuous Flow Ring-Opening Cyclization

With a set of optimized conditions for successful batch synthesis of hydropyrido[1,2-*a*]indoles **50**, **50b-c** in hand, an attempt to transfer these transformations to continuous flow was in order (Table 4.3). To our delight, CF proved to be an efficient technology for ring-opening cyclization and hydropyrido[1,2-*a*]indoles **50**, **50b-c** were

synthesized in excellent yields, comparable to the respective batch results. In fact, the continuous flow synthesis of **50**, **50c** and **50d** revealed CF to be superior to batch for those substrates. Typically, relatively low yields are obtained from the reactor after the first residence time (15 minutes) as the flow reactor approaches steady state. Thereafter, all products were obtained in near-quantitative yields at virtually all residence times (30, 45, and 60 min). In addition, these examples showcased flow ring-opening cyclizations in high throughputs (4.3-5.6 g h^{-1}), with the capability for even higher values (via easy scale-up or scale-out techniques). The successful implementation of flow technology of fast ring-opening cyclizations under sustainable reaction conditions (MeCN solvent, low catalyst loading of $In(OTf)_3$) was significant step towards sustainable scalable and cost-effective synthesis of hydropyrido[1,2-*a*]indoles.

Table 4.3. Continuous Flow Ring-Opening Cyclizations.





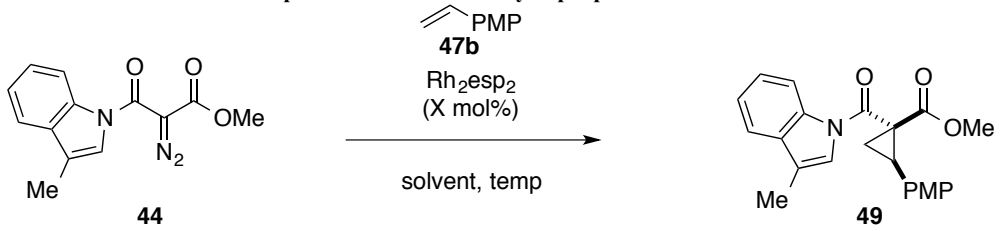
	50	**50b**	**50c**	**50c**
Reaction Conditions:	5 mol% $In(OTf)_3$ 0.1 M CH_3CN, rt	5 mol% $In(OTf)_3$ 0.1 M CH_3CN, rt	15 mol% $In(OTf)_3$ 0.1 M CH_3CN, 50 °C	5 mol% $In(OTf)_3$ 0.1 M CH_3CN, rt
	Batch: **96% yield**	Batch: **90% yield**	Batch: **99% yield**	Batch: **79% yield**
Continuous Flow:	15 min: **82% yield** 30 min: **99% yield** 45 min: **99% yield** 60 min: **99% yield**	15 min: **66% yield** 30 min: **96% yield** 45 min: **96% yield** 60 min: **95% yield**	15 min: **65% yield** 30 min: **93% yield** 45 min: **93% yield**	15 min: **76% yield** 30 min: **98% yield** 45 min: **93% yield** 60 min: **91% yield**
Throughput:	5.2 g h^{-1}	4.8 g h^{-1}	5.6 g h^{-1}	4.3 g h^{-1}

4.5.3.3 Batch Cyclopropanation

Efforts were made to optimize cyclopropanation using diazo **44** and alkene **47b** as the model system (Table **4.4**). The variables taken into account included **44**:**47b** mole ratio, catalyst loading, solvent and temperature. PhMe provided excellent reactivities (chemical yield and reaction time) for this transformation, affording up to 89% yield of the cyclopropane product **49** in 5-15 min timeframes (Table **4.4**, entries 1, 8-12). Unfortunately, PhMe had only been a moderately efficient as a solvent during the ring-opening cyclization optimization. Utilizing the same solvent for both the cyclopropanation and cyclization transformations would of immense benefit, precluding the need for tricky in-line solvent switches. Therefore, MeCN, successfully implemented in the cyclization step (both in batch and flow), was investigated. Cyclopropanation in

MeCN room temperature were sluggish and took 48 h to achieve complete conversion (Table **4.4**, entries 2-4). Temperatures of 82 °C and 50 °C, with 1.1:1 ratios of **44**:**47b**, provided faster reactions (< 20 minutes) in good yields (77% and 73%, respectively) (Table **4.4**, entries 5, 7). The lower of the two temperatures, 50 °C, and its accompanying reaction conditions were chosen as the optimized conditions (Table **4.4**, entry 7). In addition, when alpha methyl styrene (**47c**) was used as the alkene in the reaction, its respective cyclopropane **49b** was obtained in a 73% yield (Table **4.4**, entry 13).

Table 4.4. Optimization of Batch Cyclopropanation[a].



entry	**44** : **47b** ratio	catalyst loading (mol%)	solvent	temperature (°C)	time	yield [b] (%)
1	1. 1: 1	1.0	PhMe	23	< 5 min	86
2	1.1 : 1	0.1	MeCN	23	48 h	--[c]
3	1.1 : 1	0.5	MeCN	23	48 h	--[c]
4	1.1 : 1	1.0	MeCN	23	48 h	82
5	1.1 : 1	1.0	MeCN	82	< 5 min	77
6	1.1 : 1	0.1	MeCN	82	15-20 min	--[c]
7	1.1 : 1	1.0	MeCN	50	15 min	73
8	1.3 : 1	1.0	PhMe	50	15 min	83
9	1.5 : 1	1.0	PhMe	50	15 min	89
10	1 : 1.1	1.0	PhMe	50	15 min	74
11	1 : 1.3	1.0	PhMe	50	15 min	77
12	1 : 1.5	1.0	PhMe	50	15 min	77
13	1 : 1.5	1.0	PhMe	50	20 min	73[d]

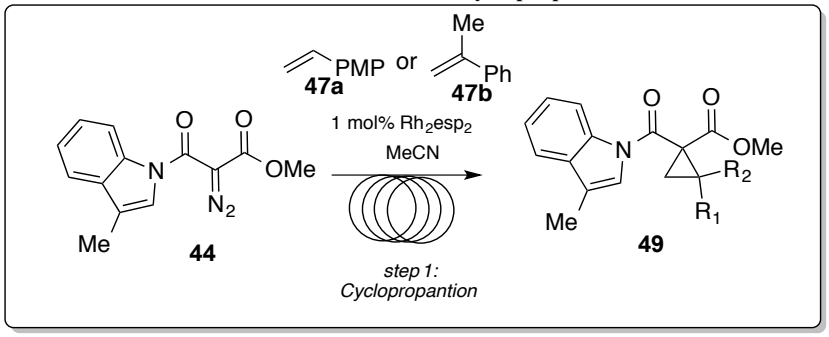
[a] Reaction run with diazo **44**, alkene **47b** and Rh_2esp_2 (X mol%) in DCM (0.2 M). [b] Isolated yields after column chromatography, major diastereomer shown, typical drs: 8.4:1 - 8.6:1. [c] Product not isolated. [d] Reaction carried out using alphamethyl styrene (**47c**) instead of alkene **47b.**

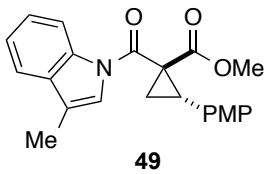
4.5.3.4 Continuous Flow Cyclopropanation

An attempt was made to carry out Rh_2esp_2-catalyzed cyclopropanations in flow (Table **4.5**). For the synthesis of cyclopropane **49**, continuous flow afforded good yields (83%, 83%, 79%) at the different residence times. These results were good agreement with the corresponding batch results (89% yield). As an added bonus, continuous flow

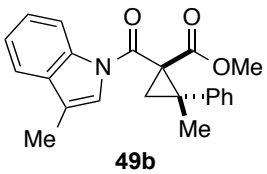
enabled a satisfactory 3.9 g h^{-1} product throughput of **49**. However, attempts to synthesize cyclopropane **49b** in flow led to modest product yields (54%, 57%, and 59%), significantly less than the corresponding batch result (73%). This disparity can be attributed to the relatively slow reaction of α-methyl styrene (**47b**), due to being both more electron-poor and sterically encumbered with respect to *p*-methoxystyrene (**47b**). Another important factor in diazo-based cyclopropanations is the generation of molecular N_2, which causes irregularities in flow rate. Typically, this effect can be mitigated through lowering the reactor flow rate; this seemed effective for the faster-reacting alkene **47a**, but not with the slower **47b**. In any case, flow chemistry still provided cyclopropane **49b** in a respectable 2.6 g h^{-1} product throughput.

Table 4.5. Continuous Flow Cyclopropanation[a].





49



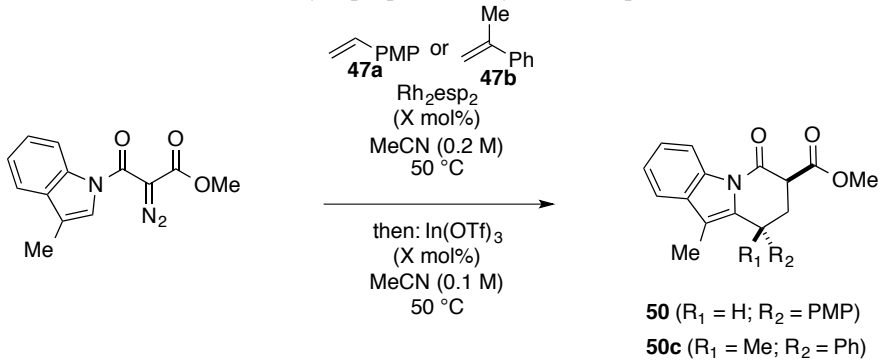
49b

Reaction Conditions:	1 mol% $Rh_2(esp)_2$ 0.2 M CH_3CN, 50 °C	1 mol% $Rh_2(esp)_2$ 0.2 M CH_3CN, 50 °C
	Batch: **89% yield**	Batch: **73% yield**
Continuous Flow:	36 min: **83% yield** 60 min: **83% yield** 90 min: **78% yield**	30 min: **54% yield** 60 min: **57% yield** 90 min: **59% yield**
Throughput:	3.9 g h^{-1}	2.6 g h^{-1}

4.5.3.5 Batch Tandem Cyclopropanation/Ring-Opening Cyclization

With the single-step transformations (cyclopropanation an ring-opening cyclization) now successfully optimized under batch conditions and transferred to flow, the penultimate goal of combining these transformations in a tandem format could now be attempted. In the batch setup, diazo **44**, Rh_2esp_2, and alkene **47a** or **47b** were mixed and reacted in an initial cyclopropanation event (Table **4.6**). Following complete conversion to the respective cyclopropane **49** or **49b**, a solution of $In(OTf)_3$ was added to the flask, directly, without any intermediary purification or workup. These tandem reactions were optimized to utilize low catalyst loading, while providing high catalyst loadings in short reaction timeframes (< 20 min per individual step). Gratifyingly, efficient and sustainable tandem cyclopropanation/cyclizations were demonstrated to be possible; optimal batch conditions for the tandem synthesis of hydropyrido[1,2-a]indole **50** (88% yield) were found to be 1 mol% Rh_2esp_2, 5 mol% $In(OTf)_3$ (Table 4.6, entry 1), while those for **50c** (91% yield) were 1 mol% Rh_2esp_2, 5 mol% $In(OTf)_3$ (Table 4.6, entry 5). In both tandem transformations, reactions has to be heated to 50 °C for efficient reactivity in suitable reaction timeframes.

Table 4.6. Tandem Cyclopropanation/Cyclization Optimization[a].



50 (R_1 = H; R_2 = PMP)
50c (R_1 = Me; R_2 = Ph)

entry	alkene	Rh_2esp_2 loading (mol%)	$In(OTf)_3$ loading (mol%)	time (t_1/t_2)	yield [b] (%)
1	**47a**	1.0	5	20 min/10 min	88
2	**47a**	0.5	5	40 min/10 min	65
3	**47a**	1.0	2.5	20 min/ 15 min	89
4	**47b**	1.0	5	20 min/20 min	33
5	**47b**	1.0	15	20min/20 min	91

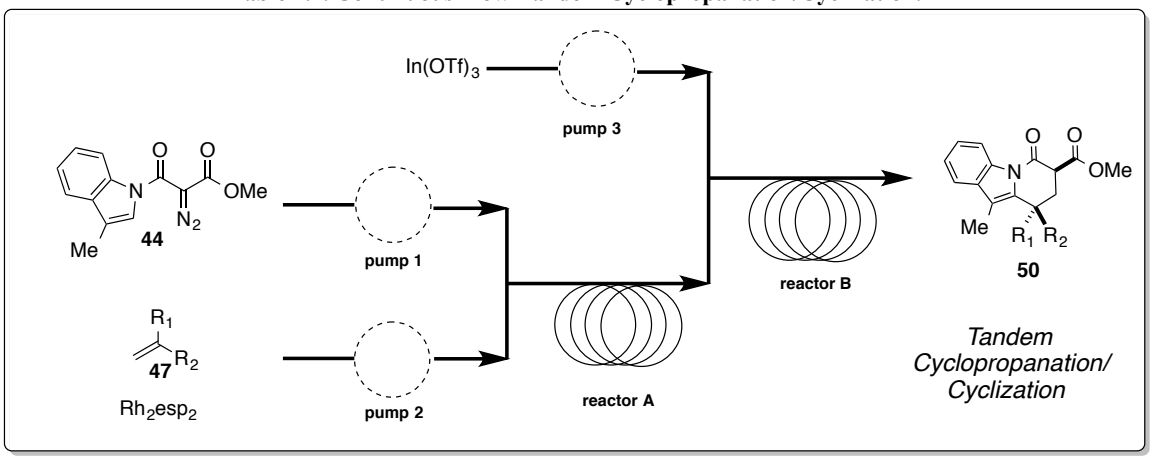
[a] Reaction run with diazo **44**, alkene **47**, Rh_2esp_2 (X mol%),$In(OTf)_3$ (X mol%) in MeCN (0.1 M).
[b] Isolated yields after column chromatography, major diastereomer shown, typical drs: 2.9:1 -3.2:1.

4.5.3.6 Continuous Flow Tandem Cyclopropanation/Ring-Opening Cyclization

With the tandem cyclopropanations/cyclizations now successfully optimized in batch, a continuous flow tandem, multistep continuous flow synthesis of hydropyrido[1,2-*a*]indoles **50** and **50c** was attempted Table 4.7). The reactor configuration featured solutions of diazo **44** (feed 1) and Rh_2esp_2/alkene **47a** or **47b** (feed 2) that were separately introduced into the reactor 1 for an initial cyclopropanation reaction. The resulting cyclopropane was fed, directly, into reactor 2 where an incoming stream of $In(OTf)_3$ (feed 3) initiated the ring-opening cyclization. This tandem continuous flow setup afforded hydropyrido[1,2-*a*]indoles **50** and **50c** directly from diazo **44** without any intermediary workup or purification. Hydropyridoindole **50** was

consistently produced in near quantitative yields (96-99%) across several residence times, and in high throughput (4.7 g h^{-1}). In this case, continuous flow clearly out-performed the respective batch outcome (88% yield). On the other hand, tandem flow synthesis of **50c** led modest yields (56-66%, 2.8 g h^{-1} throughput) that were lower than the corresponding batch result (91%). Again, a combination of slow rate of cyclopropanation coupled with flow rate irregularities due to N_2 extrusion could account for this disparity. However, in undertaking these flow tandem transformations, no in-line solvent switching or reagent scavenging were necessary.

Table 4.7. Continuous Flow Tandem Cyclopropanation/Cyclization.



	50	**50c**
Reaction Conditions:	1 mol% Rh_2esp_2 5 mol% $In(OTf)_3$ 0.1 M CH_3CN, rt	1 mol% Rh_2esp_2 15 mol% $In(OTf)_3$ 0.1 M CH_3CN, 50 °C
	Batch: **88% yield**	Batch: **91% yield**
Continuous Flow:	50 min: **96% yield** 60 min: **96% yield** 70 min: **99% yield** 80 min: **99% yield** 90 min: **99% yield**	50 min: **66% yield** 60 min: **58% yield** 70 min: **65% yield** 80 min: **56% yield** 90 min: **56% yield**
Throughput:	4.7 g h^{-1}	2.8 g h^{-1}

4.5.4 Summary: Continuous Flow Tandem Cyclopropanation/Ring-Opening Cyclization

Continuous flow technology offers many advantages over batch setups: (1) efficient temperature control and mixing; (2) easy automation; (3) safe handling of hazardous reagents/intermediates; (4) easy scale-up/scale-out on a small footprint; (5) the ability to heat reactors above the solvents' boiling points; (6) reduction of waste, (7) lowered production costs, (8) increased reaction reproducibility and enhanced product quality, and (9) the potential for uninterrupted, multi-step reaction sequences. In an effort to leverage some of these important advantages, flow chemistry was applied for the synthesis of hydropyrido[1,2-*a*]indoles. The hydropyrido[1,2-*a*]indole core features in many important indole alkaloid natural products and can be synthesized via interesting cyclopropanation/cyclization protocol. Using a strategic and streamlined approach, cyclopropanations and ring-opening cyclizations were separately optimized under batch conditions and then transferred to flow. Next, tandem cyclopropanations/cyclization were also successfully undertaken in flow. These examples represent the first examples of homo-Nazarov-type tandem cyclopropanation/ring-opening cyclization processes in flow. Generally, continuous flow led to enhanced reactivity and higher yields, with the exception of cases wherein a relatively electron-poor alkene was involved. In all cases, however, moderate to high product throughputs were obtained for both the individual steps and the tandem transformation. The successful transfer from batch to flow was also capped by use of sustainable reaction conditions: (1) MeCN as a "green" solvent for both steps; (2) low catalyst (Rh_2esp_2/ $In(OTf)_3$) loadings; (3) fast reaction times.

4.6 EXPERIMENTAL SECTION

- For supporting information (including characterization) for continuous flow tandem reactions see: Aponte-Guzmán, J.; Shenje, R.; Huang, Y.; Woodham, W. H.; Saunders, S. R.; Mostaghimi, S. M.; Flack, K. R.; Pollet, P.; Eckert, C. A.; Liotta, C. L., France, S. Tandem, Bicatalytic Continuous Flow Cyclopropanation-Homo-Nazarov-Type Cyclization. *Ind. Eng. Chem. Res.* **2015,** *54* (39), 9550-9558.

4.7 REFERENCES

1. Aponte-Guzmán, J.; Shenje, R.; Huang, Y.; Woodham, W. H.; Saunders, S. R.; Mostaghimi, S. M.; Flack, K. R.; Pollet, P.; Eckert, C. A.; Liotta, C. L., France, S. Tandem, Bicatalytic Continuous Flow Cyclopropanation-Homo-Nazarov-Type Cyclization. *Ind. Eng. Chem. Res.* **2015,** *54* (39), 9550-9558.

2. (a) Goršek, A.; Glavič, P., Design of batch versus continuous processes: Part I: single-purpose equipment. *Chem. Eng. Res. Des.* **1997,** *75* (7), 709-717; (b) McQuade, D. T.; Seeberger, P. H., Applying Flow Chemistry: Methods, Materials, and Multistep Synthesis. *J. Org. Chem.* **2013,** *78* (13), 6384-6389; (c) Löwe, H.; Ehrfeld, W., State-of-the-art in microreaction technology: concepts, manufacturing and applications. *Electrochim. Acta* **1999,** *44* (21), 3679-3689.

3. Yoshida, J.-i.; Takahashi, Y.; Nagaki, A., Flash chemistry: flow chemistry that cannot be done in batch. *Chem. Commun.* **2013,** *49* (85), 9896-9904.

4. Wegner, J.; Ceylan, S.; Kirschning, A., Ten key issues in modern flow chemistry. *Chem. Commun.* **2011,** *47* (16), 4583-4592.

5. (a) Hartman, R. L.; McMullen, J. P.; Jensen, K. F., Deciding whether to go with the flow: evaluating the merits of flow reactors for synthesis. *Angew. Chem. Int. Ed.* **2011,** *50* (33), 7502-7519; (b) Stroock, A. D.; McGraw, G. J., Investigation of the staggered herringbone mixer with a simple analytical model. *Philos. Trans. A Math. Phys. Eng. Sci.* **2004,** *362* (1818), 971-986; (c) Stone, H. A.; Stroock, A. D.; Ajdari, A., Engineering flows in small devices: microfluidics toward a lab-on-a-chip. *Annu. Rev. Fluid Mech.* **2004,** *36*, 381-411.

6. Moseley, J. D.; Woodman, E. K., Scaling-out pharmaceutical reactions in an automated stop-flow microwave reactor. *Org. Process Res. Dev.* **2008,** *12* (5), 967-981.

7. Jas, G.; Kirschning, A., Continuous flow techniques in organic synthesis. *Chem. Eur. J.* **2003,** *9* (23), 5708-5723.

8. Webb, D.; Jamison, T. F., Continuous flow multi-step organic synthesis. *Chem. Sci.* **2010,** *1* (6), 675-680.

9. Wegner, J.; Ceylan, S.; Kirschning, A., Flow chemistry–a key enabling technology for (multistep) organic synthesis. *Adv. Synth. Catal.* **2012,** *354* (1), 17-57.

10. Gilmore, K.; Seeberger, P. H., Continuous flow photochemistry. *Chem. Rec.* **2014,** *14* (3), 410-418.

11. Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J.-i., Control of extremely fast competitive consecutive reactions using micromixing. Selective Friedel-Crafts aminoalkylation. *J. Am. Chem. Soc.* **2005,** *127* (33), 11666-11675.

12. Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. i., Room‐temperature swern oxidations by using a microscale flow system. *Angew. Chem. Int. Ed.* **2005,** *44* (16), 2413-2416.

13. Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J.-i., Control of Extremely Fast Competitive Consecutive Reactions using Micromixing. Selective Friedel−Crafts Aminoalkylation. *J. Am. Chem. Soc.* **2005,** *127* (33), 11666-11675.

14. Ratner, D. M.; Murphy, E. R.; Jhunjhunwala, M.; Snyder, D. A.; Jensen, K. F.; Seeberger, P. H., Microreactor-based reaction optimization in organic chemistry—glycosylation as a challenge. *Chem. Commun.* **2005,** (5), 578-580.

15. Pastre, J. C.; Browne, D. L.; Ley, S. V., Flow chemistry syntheses of natural products. *Chem. Soc. Rev.* **2013,** *42* (23), 8849-8869.

16. (a) Sy, L.-K.; Brown, G. D., The mechanism of the spontaneous autoxidation of dihydroartemisinic acid. *Tetrahedron* **2002,** *58* (5), 897-908; (b) Sy, L.-K.; Brown, G. D., The role of the 12-carboxylic acid group in the spontaneous autoxidation of dihydroartemisinic acid. *Tetrahedron* **2002,** *58* (5), 909-923; (c) Sy, L.-K.; Brown, G. D.; Haynes, R., A novel endoperoxide and related sesquiterpenes from Artemisia annua which are possibly derived from allylic hydroperoxides. *Tetrahedron* **1998,** *54* (17), 4345-4356; (d) Sy, L.-K.; Zhu, N.-Y.; Brown, G. D., Syntheses of dihydroartemisinic acid and dihydro-epi-deoxyarteannuin B incorporating a stable isotope label at the 15-position for studies into the biosynthesis of artemisinin. *Tetrahedron* **2001,** *57* (40), 8495-8510.

17. Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T., The Continuous‐Flow Synthesis of Ibuprofen. *Angew. Chem. Int. Ed.* **2009,** *48* (45), 8547-8550.

18. Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K., A flow process for the multi-step synthesis of the alkaloid natural product oxomaritidine: a new paradigm for molecular assembly. *Chem. Commun.* **2006,** (24), 2566-2568.

19. (a) Patil, D. V.; Cavitt, M. A.; France, S., iastereoselective Synthesis of (±)-Deethyleburnamonine Using A Catalytic Cyclopropane Ring-Opening/Friedel-Crafts Alkylation Strategy (Dedicated to Dr. Albert Padwa on his 75th birthday). *Heterocycles* **2012,** *84* (2), 1363-1373; (b) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S., An

efficient synthesis of hydropyrido[1,2-*a*]indole-6(7H)-ones via an In(III)-catalyzed tandem cyclopropane ring-opening/Friedel-Crafts alkylation sequence. *Chem. Commun.* **2011,** *47* (37), 10278-10280; (c) Patil, D. V.; Phun, L. H.; France, S., Indium-Catalyzed Homo-Nazarov Cyclizations of Alkenyl Cyclopropyl Ketones. *Org. Lett.* **2010,** *12* (24), 5684-5687; (d) Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S., A Catalytic Homo-Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones. *Org. Lett.* **2011,** *13* (8), 1952-1955; (e) Aponte-Guzmán, J.; Taylor, J. E.; Tillman, E.; France, S., Catalytic, Formal Homo-Nazarov-Type Cyclizations of Alkylidene Cyclopropane-1,1-Ketoesters: Access to Functionalized Arenes and Heteroaromatics. *Org. Lett.* **2014,** *16* (14), 3788-3791; (f) Shenje, R.; Williams, C. W.; Francois, K. M.; France, S., Catalysis and Chemodivergence in the Interrupted, Formal Homo-Nazarov Cyclization Using Allylsilanes. *Org. Lett.* **2014,** *16* (24), 6468-6471.

20. (a) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H., An efficient and practical total synthesis of (+)-vincamine from L-aspartic acid. *J. Org. Chem.* **1990,** *55* (10), 3068-3074; (b) Kam, T.-S.; Sim, K.-M., Dippinine A, A New Alkaloid of the Chippiinetype From A Malayan Tabernaemontana. *Nat. Prod. Lett.* **1999,** *13* (2), 143-146; (c) Kam, T.-S.; Sim, K.-M.; Lim, T.-M., Tronocarpine, a novel pentacyclic indole incorporating a seven-membered lactam moiety. *Tetrahedron Lett.* **2000,** *41* (15), 2733-2736; (d) Kiss, B.; Karpati, E., Mechanism of action of vinpocetine. *Acta Pharm. Hung.* **1996,** *66* (5), 213-224; (e) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T., Total synthesis of (−)-mersicarpine. *J. Am. Chem. Soc.* **2010,** *132* (4), 1236-1237.

21. Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A., Green chemistry tools to influence a

medicinal chemistry and research chemistry based organisation. *Green Chem.* **2008,** *10* (1), 31-36.

CHAPTER 5 SYNTHETIC EFFORTS TOWARDS PROPOLISBENZOFURAN B

5.1 D-A cyclopropanes: an Upcoming Versatile Class of Building Blocks

Donor-acceptor (D-A) cyclopropanes are an increasingly popular subclass in the cyclopropane family of building blocks. Without the necessary activation by appropriate substituents, cyclopropane, by itself, is relatively kinetically stable and does not readily undergo a plethora of interesting transformations. On the other hand, vicinally substituting cyclopropane with donor and acceptor groups weakens the adjoining C_1–C_2 bond, allowing milder heterolytic bond scission (Figure 5.1, A).[1] Studied have shown that the more vicinal donor and acceptor substituents are on cyclopropane, the more readily it undergoes predictable ring-opening chemistry. This ring-opening event generates 1,3-dipoles, intermediates that can undergo a multitude of cyclization,[2] cycloaddition,[3] and nucleophilic addition[4] reactions (Figure 5.1, B). Consequently, D-A cyclopropanes have been utilized as precursors to 1,3-di-functionalized alkanes, bicyclic compounds, 1,2-oxazines, cyclohexanones, tetrahydropyrans, and fused heteroaromatics, among many other molecular scaffolds.[2d, 5]

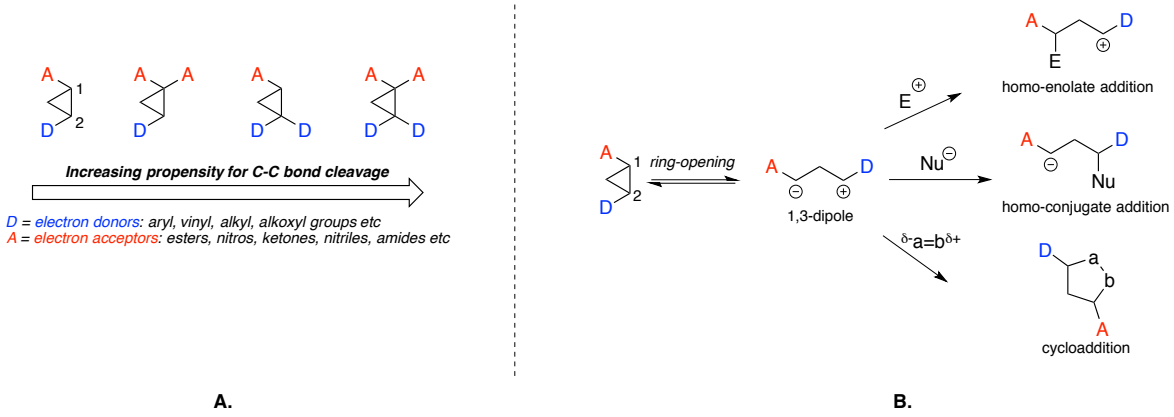
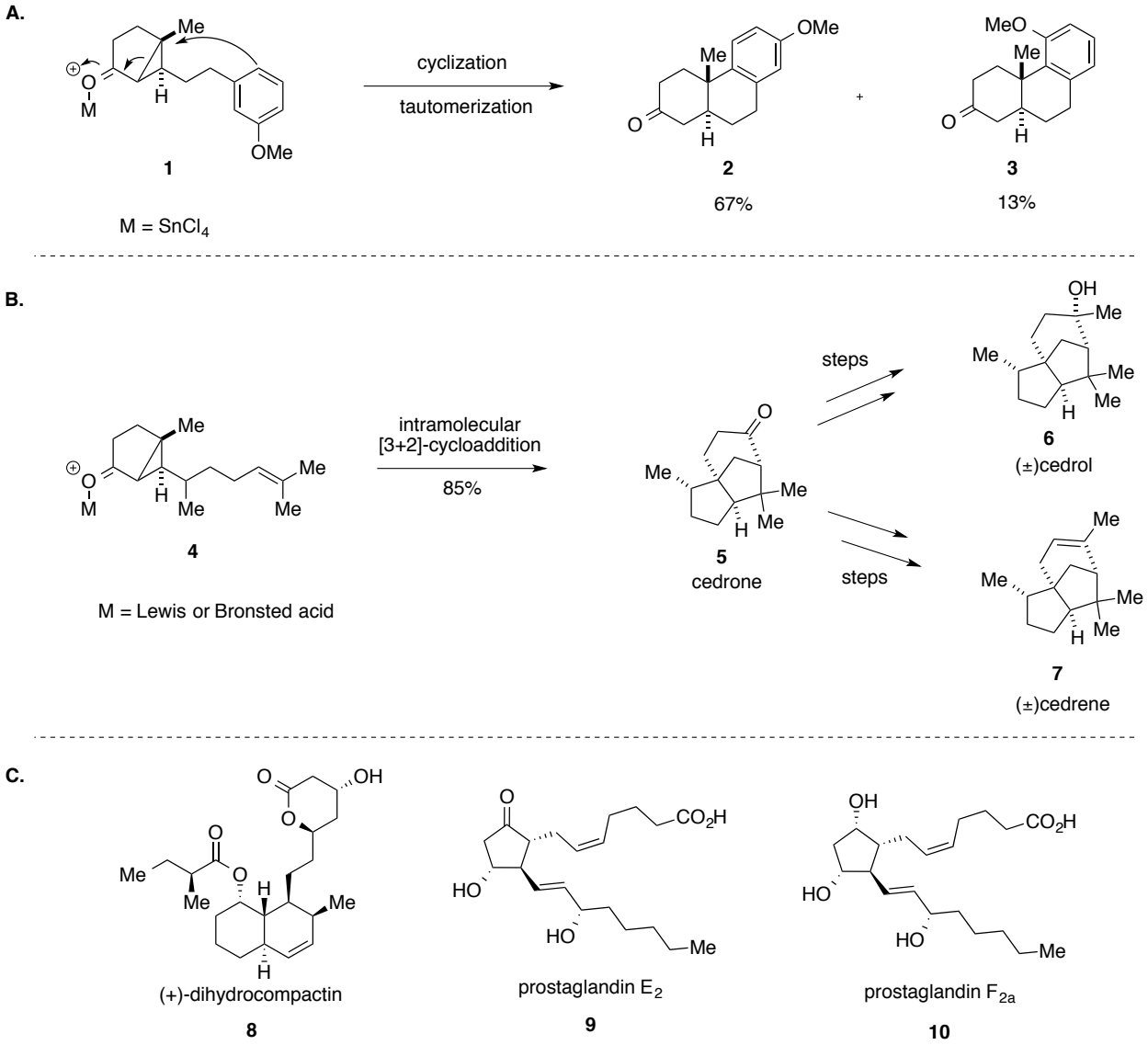


Figure 5.1. D-A Cyclopropanes as Synthetic Building Blocks.

5.2 D-A Cyclopropanes: Utility in Total Synthesis of Natural Products

Undoubtedly, D-A cyclopropanes are promising precursors for building chemical diversity. Chapter 1 highlighted the utility of D-A cyclopropanes as highly versatile building blocks that allow synthesis of many interesting chemical motifs. As further testament to their synthetic utility, D-A cyclopropanes have been incorporated in the total synthesis of natural products. More than forty years ago, Stork et. al. reported a novel D-A cyclopropane ring-opening cyclization for synthesizing interesting fused polycycles **2** and **3** (Scheme 5.1, A).[6] This methodology involved the ring-opening and cyclization of cyclopropane **1** following Lewis acid activation. Products **2** and **3** are regioisomeric and result from *para*- or *ortho*-directed Friedel-Crafts-type cyclization. Following the development of this methodology, Corey et al. were able to apply it to the total synthesis of (±)-cedrene (**7**) and (±)-cedrol (**6**) (Scheme 5.1, B).[7] In this endeavor, an intramolecular attack by the alkene of **4** leads to the formation ketone **5**, cedron. Cedron (**5**) was then used for the divergent syntheses of (±)-cedrene (**7**) and (±)-cedrol (**6**). Following these reports, Marino et. al. later applied a similar strategy for the formal synthesis of the bioactive natural product dihydrocompactin (**8**) (Scheme 5.1, C).[8] These

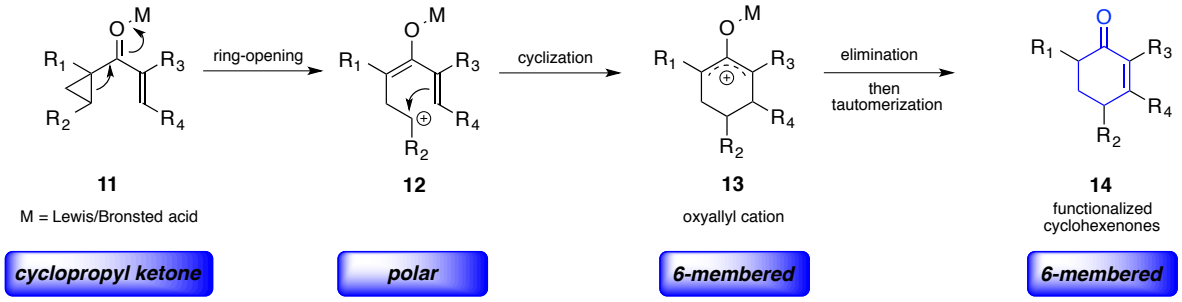
approaches ultimately inspired the synthesis of natural products such as prostaglandins E_2(**9**) and $F_{2\alpha}$(**10**) (Scheme 5.1, C).[9] Since these pioneering examples, many synthetic chemists have adopted D-A cyclopropanes for concise targeted syntheses of alkaloid, terpenoid, and steroid natural products.[1a]



Scheme 5.1. Early D-A Cyclopropane Methodologies and Their Applications.

5.3 The Homo-Nazarov Cylization: A Potential Vehicle for Total Synthesis

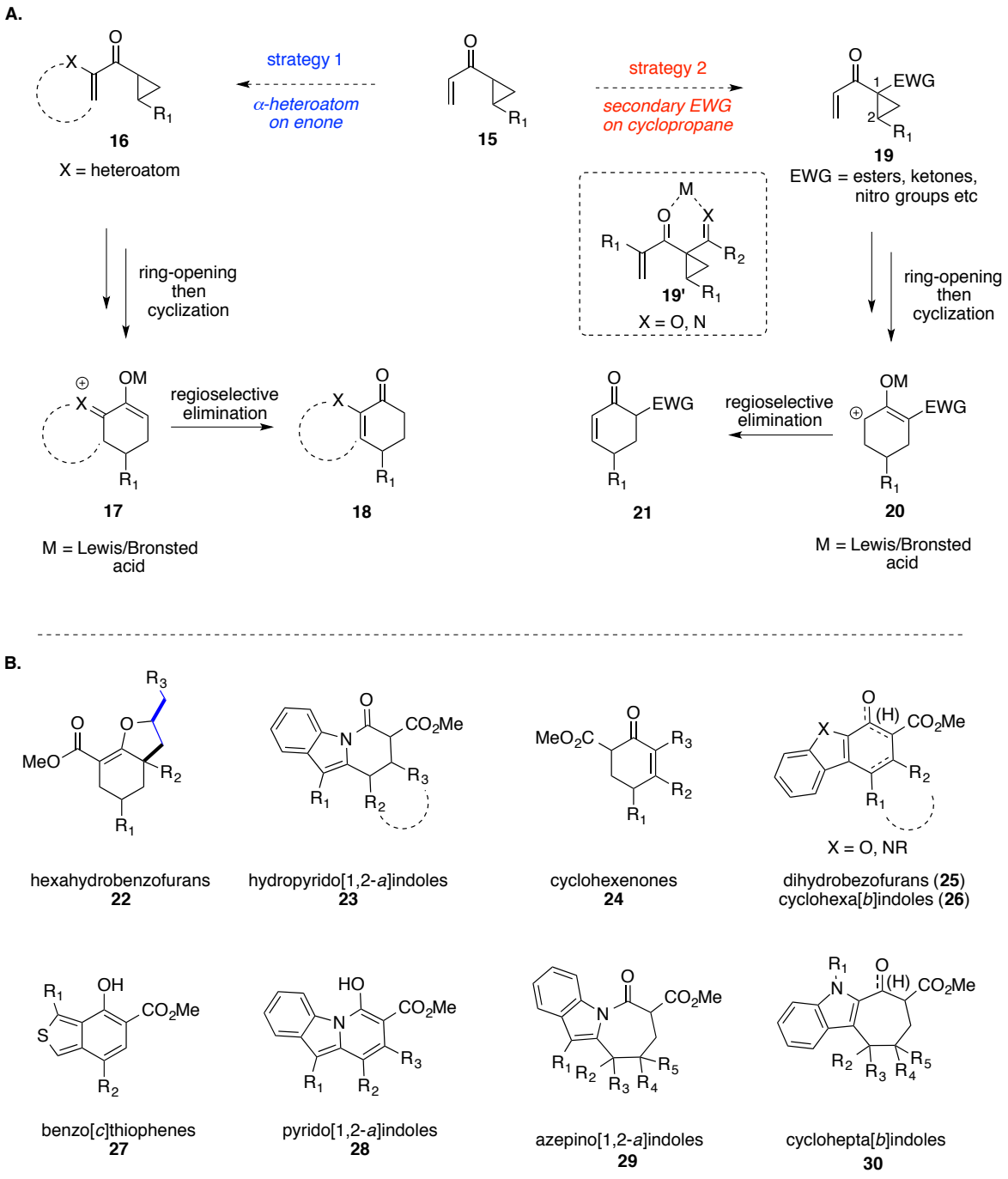
One transformation that utilizes D-A cyclopropane, the homo-Nazarov cyclization, has emerged recently and possesses much potential as a tool for chemical synthesis. Cyclopropyl vinyl ketones **11**, in the presence of Lewis or Bronsted acid promoters, undergo polar, stepwise intramolecular ring-opening cyclizations leading to the eventual formation of cyclohexenones **14** (Scheme 5.2).[2b, 10] Mechanistically, 6-membered cyclic oxyallyl cations **13** are formed in the reaction upon π–cyclization of acyclic intermediates **12**. Oxyallyl cations **13** are then subject to an elimination-tautomerization sequence to provide functionalized cyclohexenones **14**. As discussed in Chapter 2, the homo-Nazarov reaction is a relatively new transformation that has only recently started gaining popularity as viable and reliable means to rapidly build molecular complexity.



Scheme 5.2. The Homo-Nazarov Cyclization.

Early protocols of the homo-Nazarov cylization involved use of stoichiometric amounts of Lewis and Bronsted acids. Furthermore, typical activators of this transformation included $SnCl_4$ and polyphosphoric acid. The need for stoichiometric amounts of these hazardous acids was an obvious disadvantage of the homo-Nazarov reaction, making it synthetically unappealing. Recently, the France group, among others,

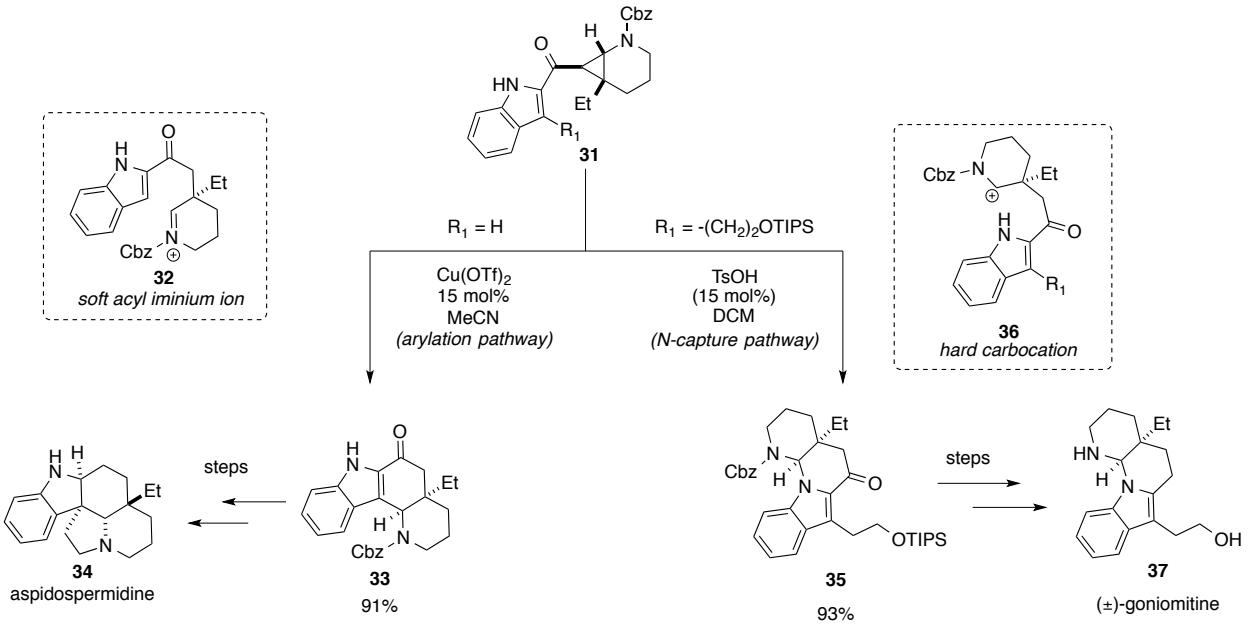
has been heavily invested method development and expansion involving homo-Nazarov cyclizations (Scheme 5.3, A).[11] Two main goals have been of particular interest: (1) need to develop milder reaction conditions for this transformation; and (2) expanding the substrate scope. These, efforts have been greatly rewarded, catalytic homo-Nazarov cyclizations have been developed, mainly through two ingenious strategies: (1) use of α-heteroatoms on the alkenyl moiety; and (2) incorporation of secondary acceptor groups. An α-heteroatom, such as in cyclopropane **16**, benefits the transformation by rendering the olefin more nucleophilic, enabling rapid capture of the carbocation formed following ring-opening (Scheme 5.3, A – strategy 1). On the other hand, installing a secondary acceptor group on the cyclopropane (depicted by substrate **19**) leads to increased polarization of the cyclopropyl C_1-C_2 bond, thus lowering the activation barrier to ring-opening (Scheme 5.3, A – strategy 2). As a result of these two strategies, homo-Nazarov reactions can now be effected under mild, catalytic conditions while also ensuring regiospecific eliminations to form only cyclohexenones **18** and **21**. Furthermore, the applicability of homo-Nazarov reactions has been expanded to a wide variety of substrates allowing access to hexahydrobenzofurans (**22**), hydropyrido[1,2-a]indoles (**23**), cyclohexenones (**24**), dihydrobenzofurans (**25**), cyclohexa[b]indoles (**26**), benzo[c]thiophenes (**27**) among others (Scheme 5.3, B).[2, 10b, 12] Other interesting derivatives of the homo-Nazarov cyclization (homo-Nazarov-inspired transformations) involving cyclobutane moieties instead of cyclopropanes and an even wider chemical space; azepino[1,2-*a*]indoles (**29**) and cyclohepta[*b*]indoles (**30**) can be synthesized.[13]



Scheme 5.3. Catalysis and Scope of the Homo-Nazarov Cyclization.

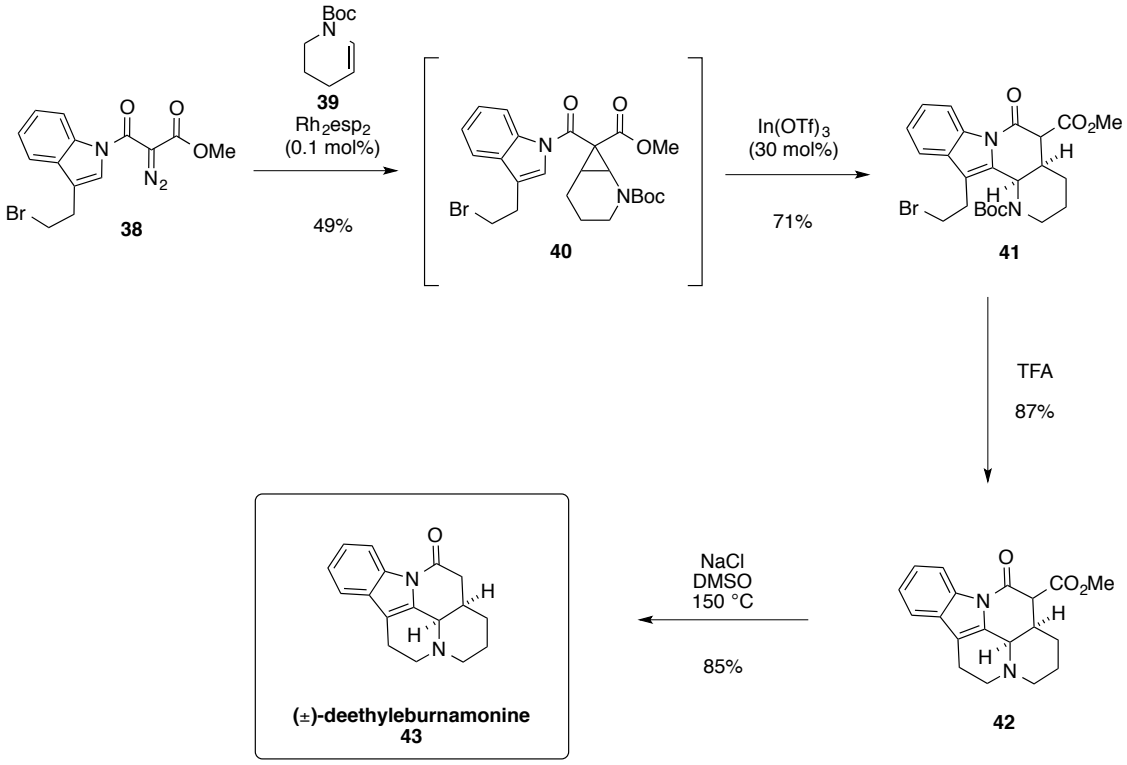
Despite the rapid progress that homo-Nazarov chemistry has experienced in the last decade, its application in the total synthesis of natural products is still limited. It is likely that the advent of catalytic homo-Nazarov and homo-Nazarov-inspired

transformations will provide an impetus for its adoption by synthetic chemists. In a recent homo-Nazarov-inspired application by Waser et al., ring-opening cyclization transformations of indole-based D-A cyclopropanes **31** were found to be catalyst-dependent leading to interesting chemodivergence (Scheme 5.4).[14] Under soft Lewis acid catalytic conditions, specifically $Cu(OTf)_2$, an arylative ring-opening cyclization occurred, efficiently, leading to the formation of cyclohexa[*b*]indole **33**. Subsequent Cbz deprotection of **33** concluded the concise, formal synthesis of the natural product aspidospermidine (**34**),[15] a proven anticancer agent. On the other hand, Bronsted acid conditions (using catalytic TsOH) afforded hydropyridoindole **35** via an *N*-capture pathway.[14] Hydropyridoindole **35** required only a few steps to accomplish the total synthesis of another anticancer compound, (±)-goniomitine (**37**). Presumably, the differential in cyclization pathways is due to whether acyl iminium intermediate **32** is formed in the transformation. The soft $Cu(OTf)_2$ Lewis acid was hypothesized to favor the formation of this intermediate which, in turn, led to cyclization via the softer indole C3 position. Conversely, a *hard-hard* interaction is experienced in the case of TsOH, where the *N*-atom quenches an intermediate carbocation on the piperidine ring in intermediate **36**.



Scheme 5.4. Waser's Homo-Nazarov-Inspired Synthesis of Natural Products.

Another homo-Nazarov-inspired approach was used by France and co-workers led to a concise and efficient total synthesis of deethyleburnamonine (**43**) (Scheme 5.5).[12a] An initial Rh_2esp_2-catalyzed cyclopropanation in the presence of enamide **39** afforded putative cyclopropane **40**. This cyclopropane was then subjected to homo-Nazarov conditions (30 mol% $In(OTf)_3$) leading to its cycloisomerization to hydropyrido[1,2-*a*]indole **41**. Subsequent TFA-induced deprotection-intramolecular cyclization led to pentacycle **42**. Finally, a Krapcho decarbalkoxylation afforded the desired natural product, deethyleburnamonine (**43**). Using this concise six-step linear sequence, deethyleburnamonine (**43**) was synthesized in an impressive 18% overall yield, a significant improvement over other approaches to the same molecule.[16]



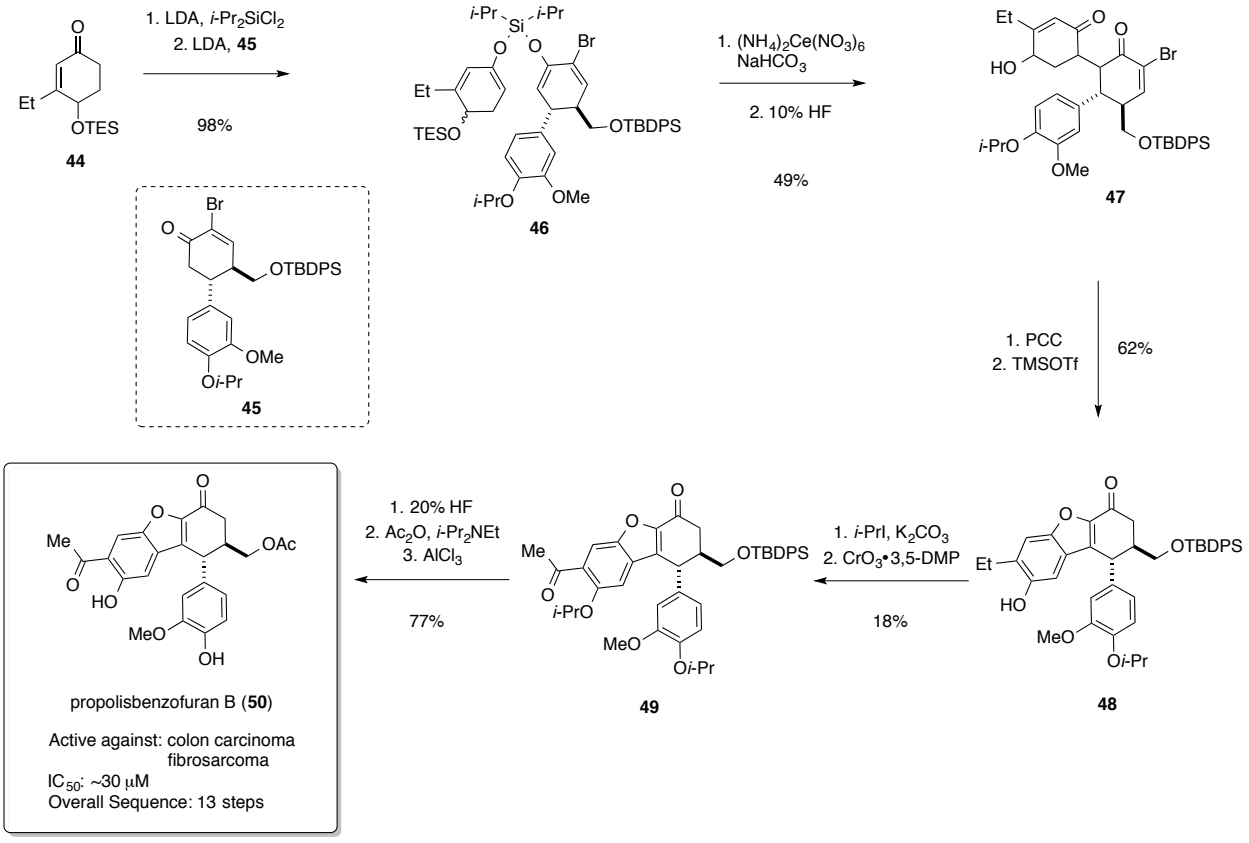
Scheme 5.5. France's Homo-Nazarov-Inspired Synthesis of Deethleburnamonine.

5.4 Synthetic Efforts Towards Propolisbenzofuran B

5.4.1 Thomson's Propolisbenzofuran B Synthesis

Propolisbenzofuran B (**50**), a natural product first isolated from Brazilian propolis by Banskota and co-workers, has been documented to be moderately cytotoxic against 26-**L**5 carcinoma and human HT-1080 fibrosarcoma cells (Scheme 5.6).[17] Structurally, propolisbenzofuran B (**50**) features an interesting and unusually decorated tricyclic dihydrobenzofuran core appended with an electron-rich aryl group. Fascinated by the structure of propolisbenzofuran B, Thomson and co-workers embarked on its total synthesis (Scheme 5.6).[17a] Enone **44**, formed via a three-step protocol, was subjected to silyl enol ether-formation conditions in the presence of LDA to furnish silyl bis-enol ether **46**. This step involved a reaction with previously prepared enone **45**. An oxidative coupling of silyl ether **46** under ceric ammonium nitrate conditions provide 1,4-diketone

47. PCC and TMSOTf conditions induced a benzofuran annulation of diketone **47** to afford benzofuran **48**. Phenol protection using *i*-PrI followed by a CrO_3•3,5-DMP benzylic oxidation furnished **49**. Finally, a three-step protocol involving silyl deprotection using 20% HF, acetylation of the resulting alcohol in the presence of Ac_2O, and $AlCl_3$-removal of the isopropyl ether protecting groups enabled the formation of propolisbenzofuran B (**50**). The complete sequence of propolisbenzofuran B synthesis was accomplished in 13 steps (longest linear sequence).

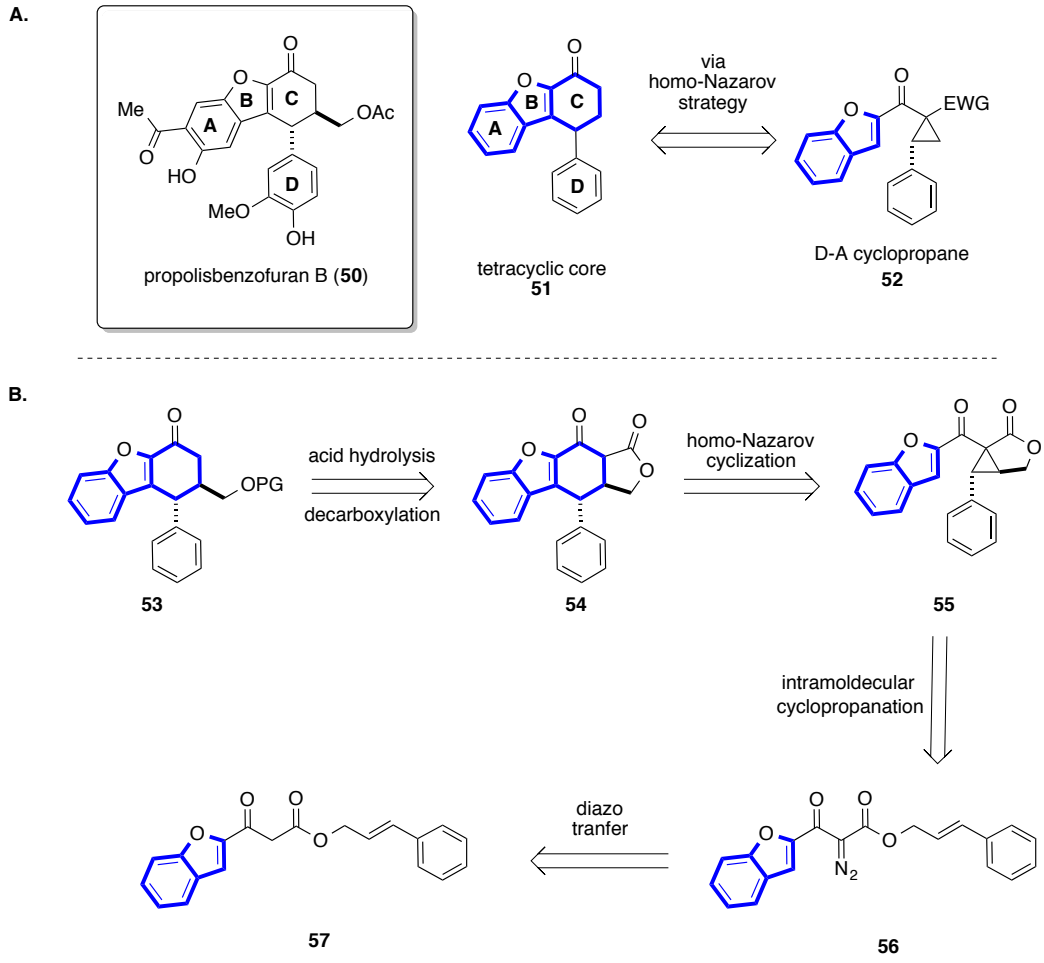


Scheme 5.6. Thomson's Propolisbenzofuran B Synthesis.

5.4.2 France Group's Homo-Nazarov Strategy Towards Propolisbenzofuran B

Thomson's 13-step protocol heralded the first total synthesis of propolisbenzofuran B in literature. Despite this accomplishment, several drawbacks from

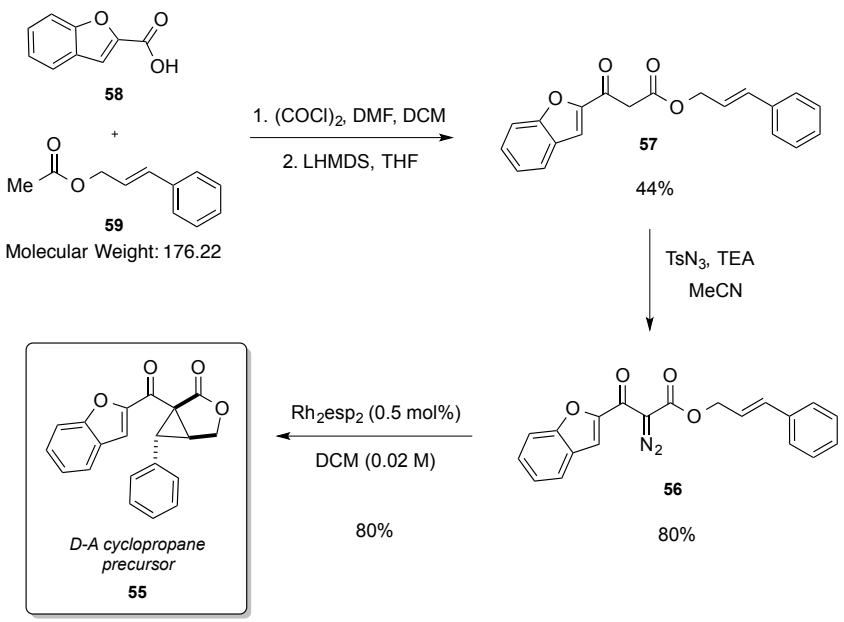
this synthesis were apparent: (1) long synthetic sequence given the structural simplicity of **50**; (2) arduous use of protection/deprotection strategies; (3) several inefficient and low-yielding steps were encountered.[17a] A more concise and efficient synthetic strategy towards propolisbenzofuran B would be beneficial to the synthetic community. Given its contiguous, tricyclic core (**51**) that is appended by an additional aryl group, propolisbenzofuran B rendered itself a potentially viable target for homo-Nazarov chemistry (Scheme 5.7, A). A retrosynthetic analysis, featuring a concise homo-Nazarov strategy, was in order (Scheme 5.7, B). As a starting point, propolisbenzofuran B was stripped of its peripheral functional group decoration to leave a reasonable truncated model system **53**. Conceivably, model system **53** would be derived from fused lactone **54** through an acid-promoted hydrolysis-decarboxylation strategy. Importantly, lactone **54** would result from the catalytic homo-Nazarov cyclization of densely functionalized D-A cyclopropane **55**. A strategic intramolecular cyclopropanation of *E*-alkene-tethered diazo **56** would provide the requisite D-A cyclopropane **55**. Diazo **56** would be obtained, in turn, from β-keto ester **57** via a diazo transfer reaction. Overall, this strategy would showcase the utility of homo-Nazarov approaches for total synthesis while also providing a potentially more concise route (with respect to Thomson's approach) to propolisbenzofuran B.



Scheme 5.7. Homo-Nazarov Approach to Propolisbenzofuran B.

5.4.2.1 Synthesis of D-A Cyclopropane 55

Acid **58** was subjected to acid chloride-forming conditions ($(COCl)_2$; cat. DMF) and the acid chloride formed therein was added to the enolate of acetate **59** (formed from a LHMDS deprotonation) (Scheme 5.8). The resulting β-keto ester **57** was then subjected to a diazo transfer protocol that afforded diazo **56** in 80% yield. Gratifyingly, a cyclopropanation event under catalytic Rh_2esp_2 conditions led to D-A cyclopropane **55** in 80% yield as a single diastereomer.

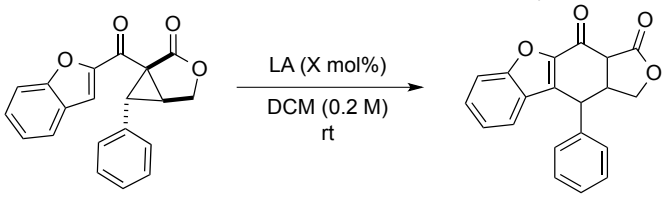


Scheme 5.8. Synthesis of D-A Cyclopropane Precursor.

5.4.2.2 Optimization of homo-Nazarov Cyclization for Propolisbenzofuran B Core

With the requisite D-A cyclopropane **55** in hand, optimization of its homo-Nazarov cyclization to the core of propolisbenzofuran B, **54**, commenced. Traditionally, strongly Lewis acidic and highly oxophilic metal salts have provided the best results for ring-opening cyclization in the homo-Nazarov cyclization. With that in mind, an initial Lewis acid screen was performed (Table 5.1). $In(OTf)_3$, at a 5 mol% loading, provided the desired product **54** in 49% (Table 5.1, entry 1) while increasing its loading to 10 mol% led to an intractable mixture of desired and by-products (Table 5.1, entry 2). $Sc(OTf)_3$ at a loading of 10 mol% provided homo-Nazarov product **54** in a 49% yield. Importantly, 1:1 mixture of $Ca((NTf)_2)_2$ and *n*-Bu_4NPF_6 (10 mol% each) outperformed all other Lewis acids, smoothly providing **54** in 63% yield (Table 5.1, entry 6). All other Lewis acids attempted led to no reactivity, decomposition or intractable reaction mixtures.

Table 5.1. Lewis Acid Screen for Homo-Nazarov Cyclization[a].



55 **54** *keto-enol*

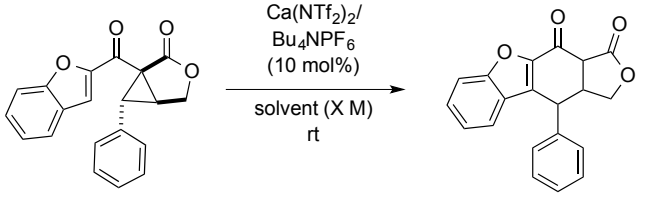
entry	LA	X (mol%)	time (h)	yield (%)
1	$In(OTf)_3$	5	3	49
2	$In(OTf)_3$	10	4	--
3	$Sc(OTf)_3$	10	4	49
4	$Al(OTf)_3$	10	24	--
5	$Hf(OTf)_4$	10	3	--
6	$Ca(NTf_2)_2$/ Bu_4NPF_6	10	3	63
7	$Ca(NTf_2)_2$/ Bu_4NPF_6	5	13	--
8	$Cu(OTf)_2$	10	24	--

[b] these Lewis acids led to degradation and/or intractable reaction outcomes. All other Lewis acids employed did not afford any of the desired products

A follow-up solvent screen and concentration optimization was performed. DCM and 1,2-DCE were clearly the best solvents for this transformation, giving yields of 63% and 44% respectively (Table 5.2, entries 1, 2). Other solvents investigated completely stalled the transformation, either through sequestration of the catalyst or inability to dissolve cyclopropane **55** and/or catalyst. A further investigation of concentration effects in DCM indicated 0.2 M to be optimum (Table 5.2, entry 1). Thus, the optimized conditions for the homo-Nazarov cyclization of D-A cyclopropane **55** to cyclohexenone **54** were: 10mol% $Ca((NTf)_2)_2$/*n*-Bu_4NPF_6 in DCM at cyclopropane concentration of 0.2 M. The successful cycloisomerization of D-A cyclopropane **55** to a simplified model

system for the core of propolisbenzofuran B validated the potential of a homo-Nazarov cyclization approach to the total synthesis of propolisbenzofuran B.

Table 5.2. Solvent and Concentration Optimization[a].



55 **54** *keto-enol*

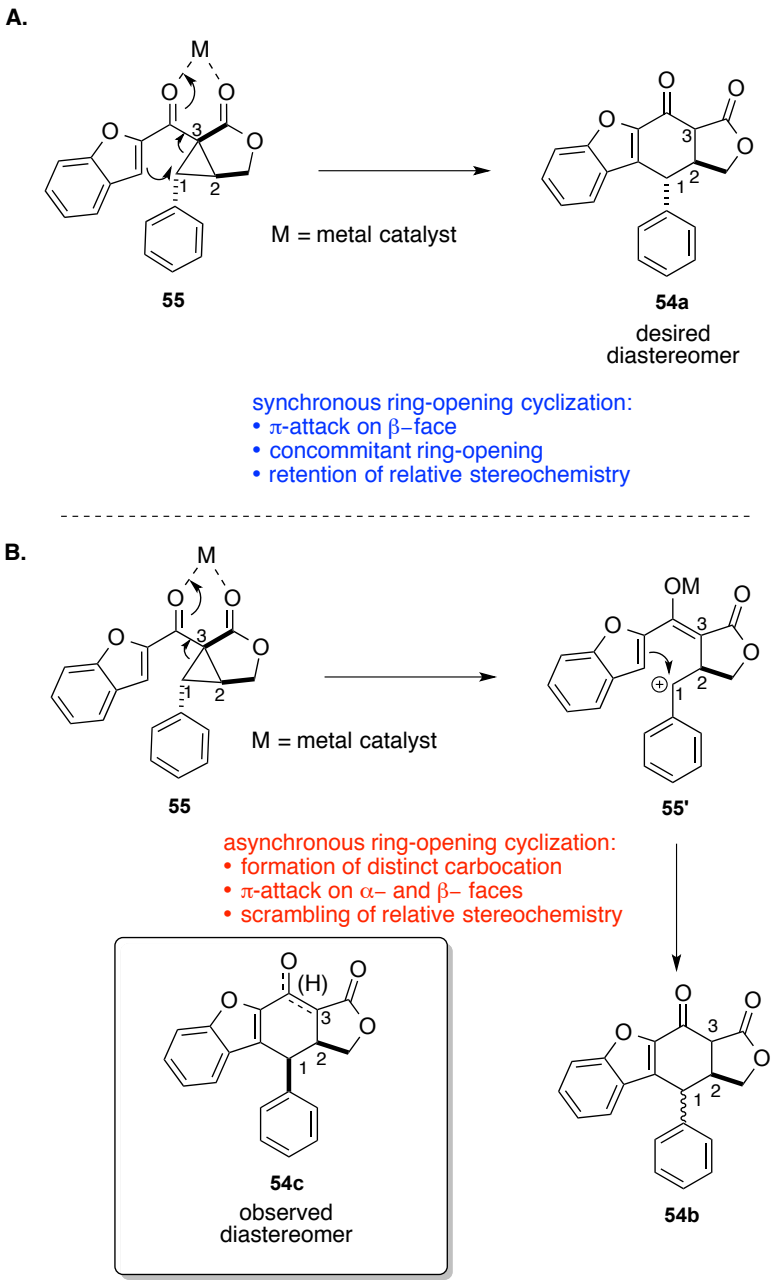
entry	solvent	conc. (M)	time (h)	yield (%)
1	DCM	0.2	3	63
2	1,2-DCE	0.2	4	44
3	MeCN	0.2	24	--
4	Acetone	0.2	24	--
5	EtOAc	0.2	24	--
6	DCM	0.5	1	38
7	DCM	0.1	8	24
8	DCM	0.05	18	31

[b] these Lewis acids led to degradation and/or intractable reaction outcomes. All other Lewis acids employed did not afford any of the desired products

5.4.2.3 Stereochemical Outcomes for Ring-Opening Cyclization

It had been hoped that used of a D-A cyclopropane **55**, featuring a *trans* relationship between groups C_1 and C_2 would potentially afford cyclohexanone **54a**, wherein the same stereochemical relationship was maintained (Scheme 5.9, A). Such stereo-transfer would likely arise from a significant degree of synchronicity in the ring-opening cyclization step, during which build-up of positive charge at carbon C_1 (as the C_1-C_2 bond began to cleave) rapidly induced a concomitant π-attach from the pendant

benzofuran. Synchronous cyclopropane ring-opening cyclizations are possible and have been explored in literature.[1b] However, experimental evidence indicated that diastereomer **54c**, featuring a *cis* configuration between C_1 and C_2, was the preferred product from the homo-Nazarov cyclization of cyclopropane **55**. This result points towards a highly asynchronous ring-opening cyclization process, whereby a distinct carbocation on C_1, in intermediate **55'**, is formed during the transformation (Scheme 5.9, B). The planarity of carbocation **55'** ensures the possibility of π-attack from either face, a feature that results in loss of stereochemical fidelity. This stereochemical outcome, while disappointing, did not necessarily rule out homo-Nazarov chemistry as potential pathway to the synthesis of propolisbenzofuran B. In light the observed stereochemical outcome, a plausible set strategies going forward can be envisaged: (1) synthesis of *epi*-propolisbenzofuran B; and (2) incorporating an epimerization event whereby synthesis of propolisbenzofuran B can still be undertaken. Of note was the fact that homo-Nazarov product **54c**, bearing a β-keto ester moiety, underwent rapid tautomerization and existed as a keto-enol mixture (in $CDCl_3$, the NMR solvent). In any case, stereochemistry at C_3 was inconsequential; a later decarboxylation would remove that stereo center.

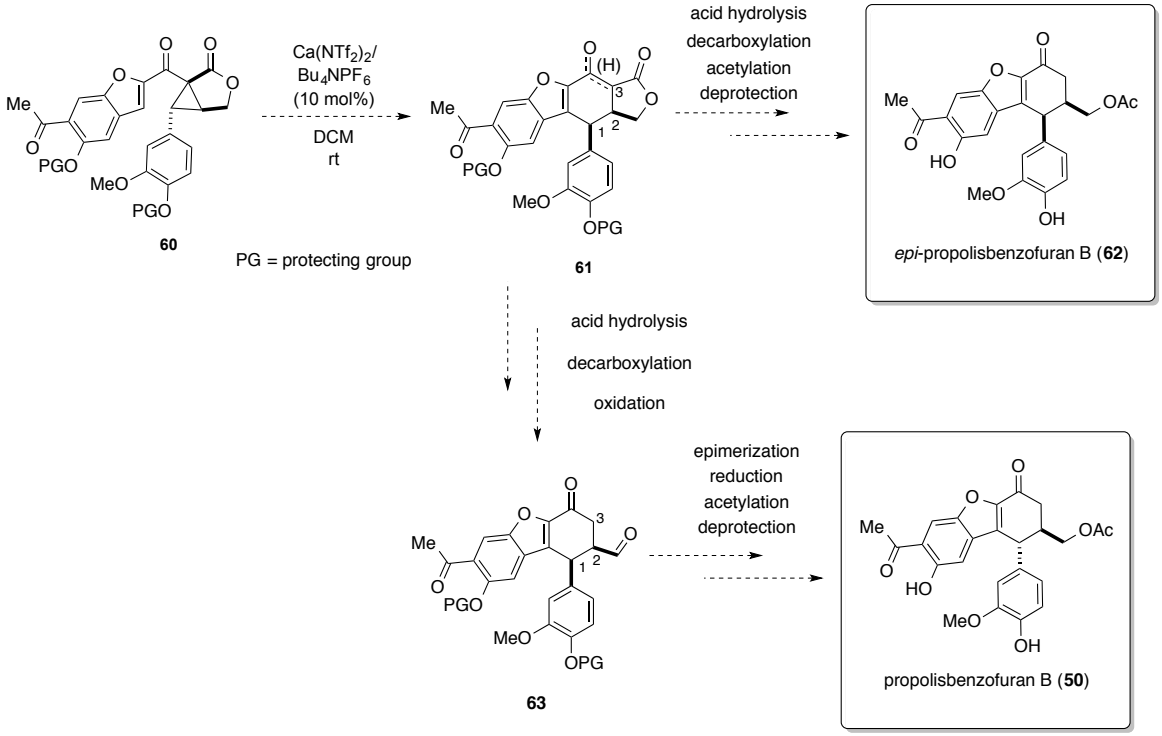


Scheme 5.9. Impact of Ring-Opening Cyclization Synchronicity on Stereochemistry.

5.4.2.4 Summary and Conclusion: Synthetic Efforts Towards Propolisbenzofuran B

A homo-Nazarov cyclization protocol for accessing the core of propolisbenzofuran was developed. A highly diastereoselective intramolecular

cyclopropanation provided the lactone-fused D-A cyclopropane needed for the cyclization. The homo-Nazarov protocol itself required 10 mol% $Ca((NTf)_2)_2$/*n*-Bu_4NPF_6. Given the successful validation of this homo-Nazarov strategy on a model system, its application to the total synthesis of propolisbenzofuran be can now be envisioned (Scheme 5.10). In light of the stereochemical outcome of this transformation, *epi*-propolisbenzofuran B (**62**) can conceivably be synthesized from **61**, the potential homo-Nazarov outcome of fully elaborated D-A cyclopropane **60**. The total synthesis of propolisbenzofuran B (**50**) itself would be completed by including an epimerization step (on aldehyde **63**) to set the required *trans* relationship at positions C_1 and C_2. This divergent approach to *epi*- and propolisbenzofuran B would be benefit the synthetic community by showcasing the enormous potential of the homo-Nazarov cyclization in natural products total synthesis.



Scheme 5.10. Potential Syntheses of *Epi*- and Propolisbenzofuran via Homo-Nazarov Strategy.

5.4.3 EXPERIMENTAL SECTION

5.4.3.1 General Methods

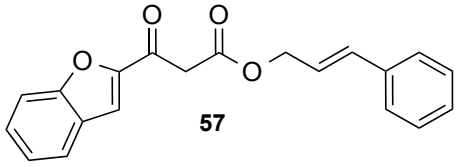
Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm) or preparative thin-layer chromatography (prep-TLC) using Silicycle silica gel F_{254} (1000 μm) plates and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp and by attenuated total reflection (ATR) through a diamond plate on a Bruker Optics Alpha-P FTIR spectrometer or using a Shimadzu IRAffinity-1S FTIR with a Specac Quest ATR attachment. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, or Bruker 400 MHz and 500 MHz spectrometers with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer using $PhCF_3$ as an external standard. ^{1}H and ^{19}F NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Mass spectra were obtained MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of

10,000 using PFK (perfluorokerosene) as an internal calibrant. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

Yields refer to isolated yields of analytically pure material unless otherwise noted. All reactions were carried out in oven-dried glassware under an atmosphere of N_2, unless stated otherwise. Tetrahydrofuran and Diethyl ether were distilled from a sodium/benzophenone ketyl under N_2 and stored in a Schlenk flask. 1,2-dichloroethane and dichloromethane was purified by distillation from calcium hydride under N_2 prior to use. Acetonitrile was dried by fractional distillation over CaH_2. Benzene was purified by drying with CaH_2. Nitromethane was distilled over CaH_2 and stored under nitrogen under 4Å molecular sieves. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification unless otherwise noted.

Synthesis of keto ester 57

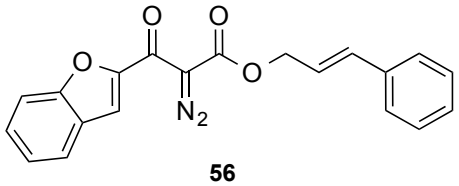


57

To a solution of acid **58** (1.0 g, 6.16 mmol) in DCM (20 mL) was added oxalyl chloride (0.64 mL, 7.40 mmol) and 2 drops of DMF. The reaction was allowed to run for 3 hours after which the mixture was concentrated under reduced pressure and re-dissolved in 20 mL of THF. This solution was added to the enolate of ester **59** [formed from reaction of ester **59** (1.14 g, 6.47 mmol) in THF (20 mL) and LiHMDS (1 M, 12.95 mL, 12.95 mmol)]. The reaction mixture was stirred for 1 h and quenched with aq. ammonium chloride, and extracted three times with EtOAc. The combined organic layers

were dried with Na_2SO_4, and purified by silica gel column chromatography (eluting with EtOAc/hexane). Keto-ester **57** was obtained as a yellow oil (861.3 mg, 44% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 12.06 (s, 0.23H), 7.74 - 7.21 (m, 15.45H), 6.77 - 6.58 (m, 1.53H), 6.40 - 6.18 (m, 1.54H), 5.93 (s, 0.27H), 4.89 (dd, *J*=1.3, 6.3 Hz, 0.57H), 4.83 (dd, *J*=1.3, 6.4 Hz, 2.03H), 4.74 (dd, *J*=1.3, 6.4 Hz, 0.35H), 4.04 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 182.9, 166.7, 155.9, 134.7, 128.8, 128.7, 128.6, 128.2, 126.7, 124.2, 123.6, 122.9, 122.4, 114.2, 112.6, 111.7, 108.9, 66.1, 45.9.

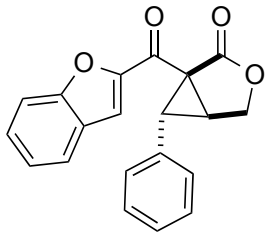
Synthesis of diazo 56



56

To a solution of keto-ester **57** (0.863 g, 2.69 mmol) in MeCN (20 mL) was added TsN_3 (0.636 g, 3.2 mmol) and Et_3N (0.449 mL, 3.2 mmol) and the reaction was stirred for 18 h. Purification by silica gel column chromatography (eluting with EtOAc/hexane) afforded diazo **56** was obtained as a yellow oil (742 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.86 (d, *J*=0.9 Hz, 1H), 7.74 - 7.69 (m, 1H), 7.59 - 7.53 (m, 1H), 7.47 (s, 1H), 7.43 - 7.38 (m, *J*=1.3 Hz, 2H), 7.37 - 7.27 (m, 3H), 6.72 (d, *J*=15.8 Hz, 1H), 6.33 (td, *J*=6.5, 15.9 Hz, 1H), 4.96 (dd, *J*=1.2, 6.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 172.28, 160.79 (s, 2C), 155.10 (s, 2C), 150.59, 135.97 - 135.79 (m, 3C), 135.48 - 135.31 (m, 5C), 128.75 - 128.55 (m, 8C), 128.36 (s, 5C), 128.31 (s, 4C), 126.91 (s, 2C), 126.73 (s, 9C), 124.00 (s, 4C), 123.42 (s, 4C), 122.17 (s, 3C), 115.16 (s, 3C), 112.29 (s, 4C), 66.33 (s, 3C).

Synthesis of cyclopropane 55



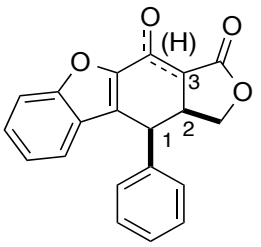
55

To a solution of diazo **56** (0.1 g, 0.29 mmol) in DCM (13.1 ML) was added Rh_2esp_2 (1 mg, 0.0013 mmol). The reaction was stirred for 3 h, concentrated under reduced pressure and purified by alumina gel column chromatography (eluting with EtOAc/hexane) to afford cyclopropane **55** was obtained as a yellow solid (73.1 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.68 - 7.62 (m, 1H), 7.49 - 7.36 (m, 2H), 7.27 - 7.19 (m, 1H), 7.18 - 7.05 (m, 4H), 4.63 - 4.55 (m, 1H), 4.45 (d, *J*=9.4 Hz, 1H), 3.51 (t, *J*=5.1 Hz, 1H), 3.05 (d, *J*=5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 178.29 (s, 2C), 170.84, 155.83 (s, 3C), 151.41 (s, 2C), 131.60 (s, 3C), 128.98 (s, 5C), 128.66 (s, 9C), 128.16 (s, 4C), 127.69 (s, 12C), 127.02 - 126.83 (m, 4C), 123.90 (s, 6C), 118.70 (s, 2C), 112.47 (s, 5C), 68.26 (s, 4C), 44.53 (s, 3C), 38.16 (s, 5C), 26.32 (s, 5C).

5.4.3.2 General Procedure for the homo-Nazarov Cyclization Synthesis of 54c

A round-bottom flask was charged with the appropriate amount of Lewis acid catalyst and cyclopropane **55** (0.3 mmol scale). The appropriate solvent was added to the flask and the reaction was stirred until complete conversion. Reactions that did not afford any conversion in 24 h were discarded. Upon complete conversion, reaction mixture was concentrated under reduced pressure and purified using either alumina gel column chromatography or silica gel preparative-TLC (eluting with EtOAc/hexane).

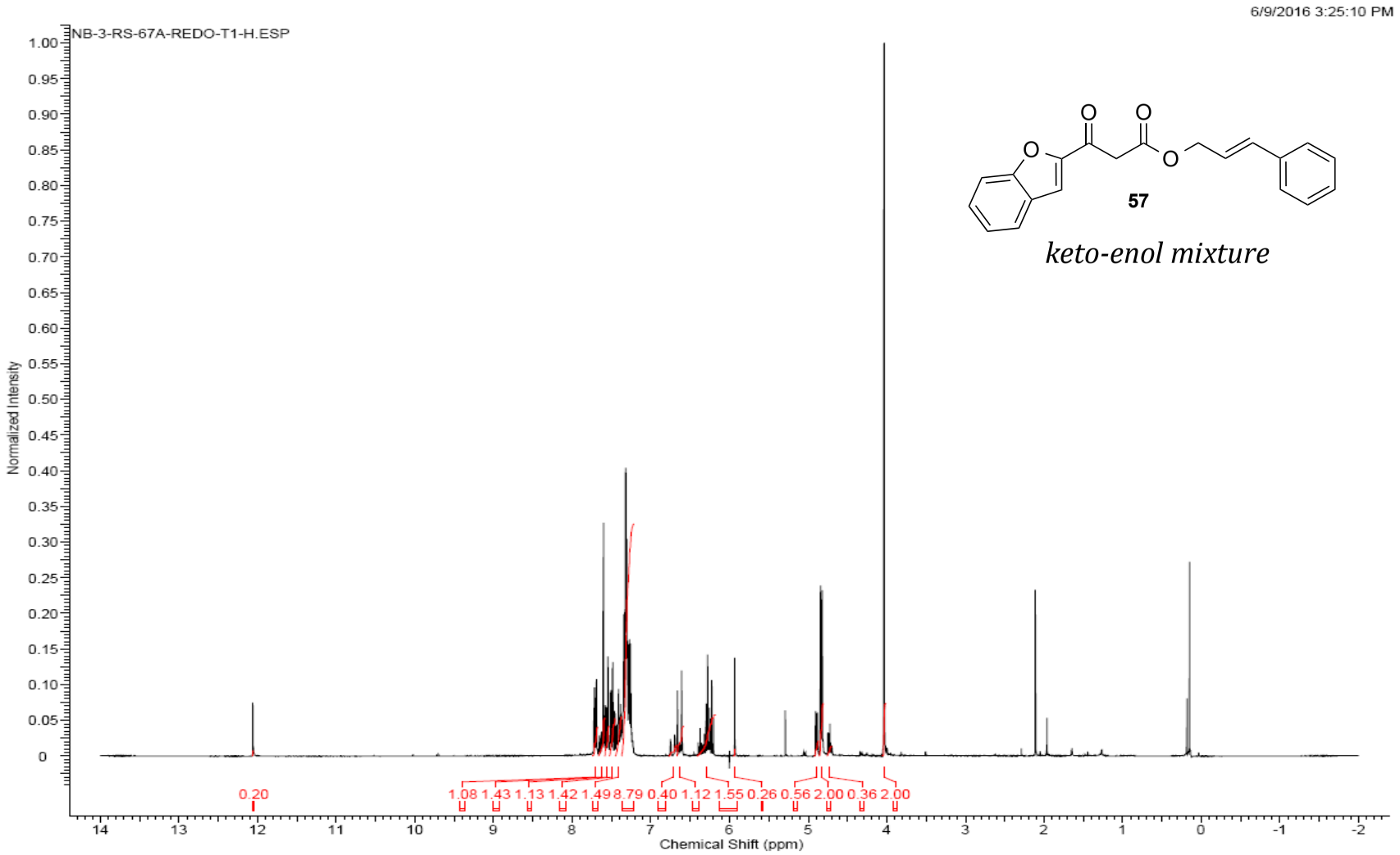
Synthesis of pentacycle 54c

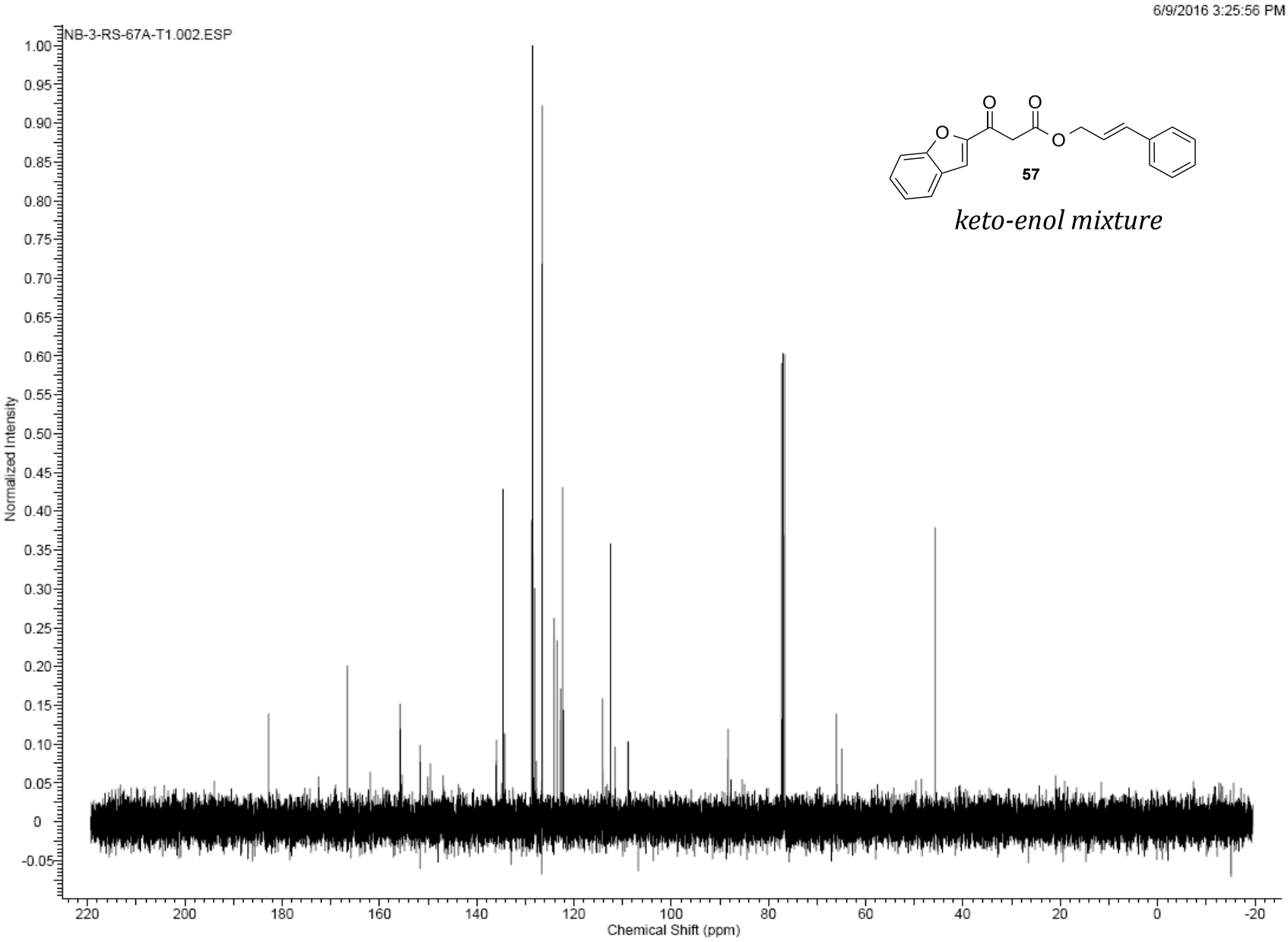


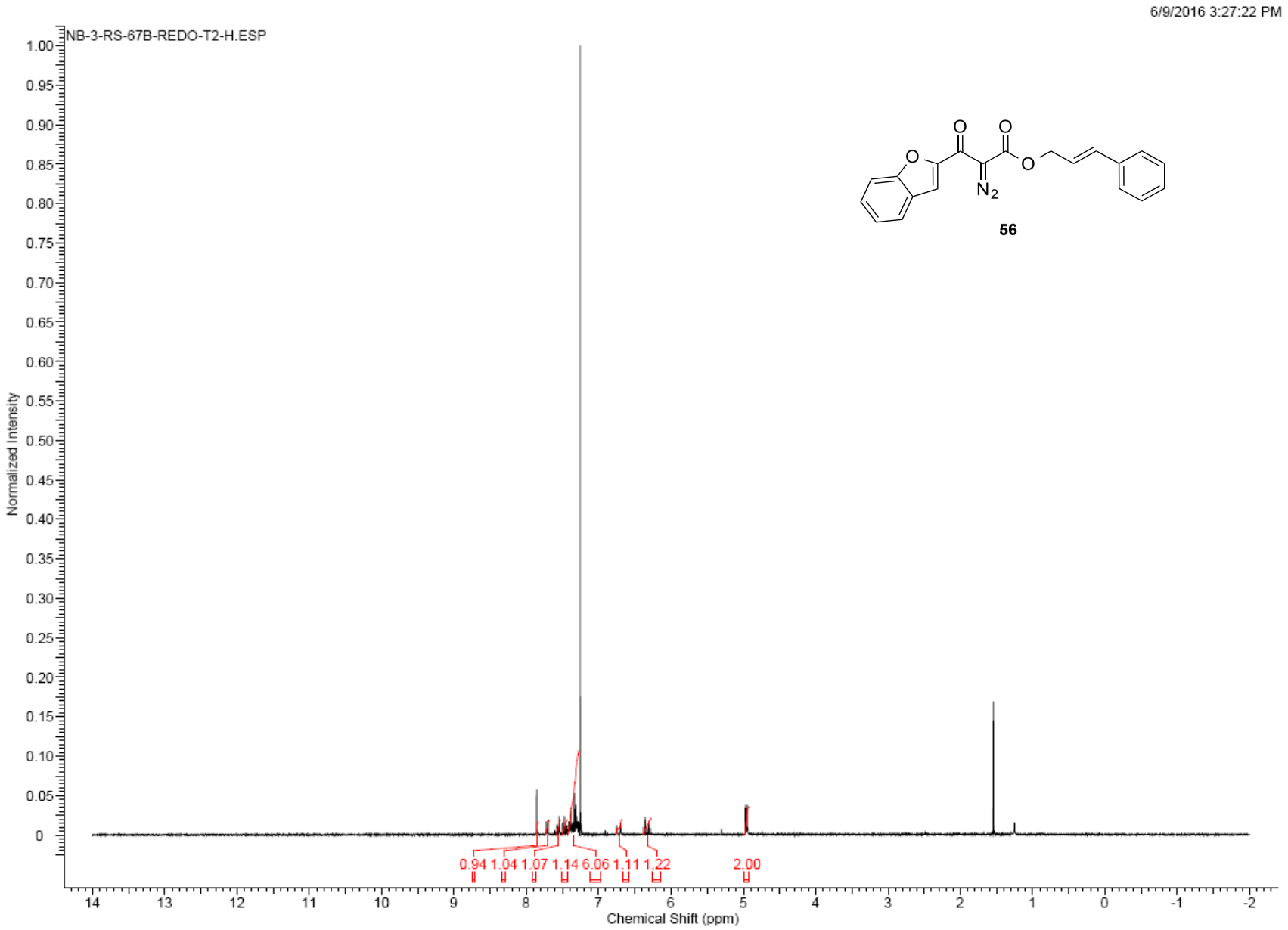
54c

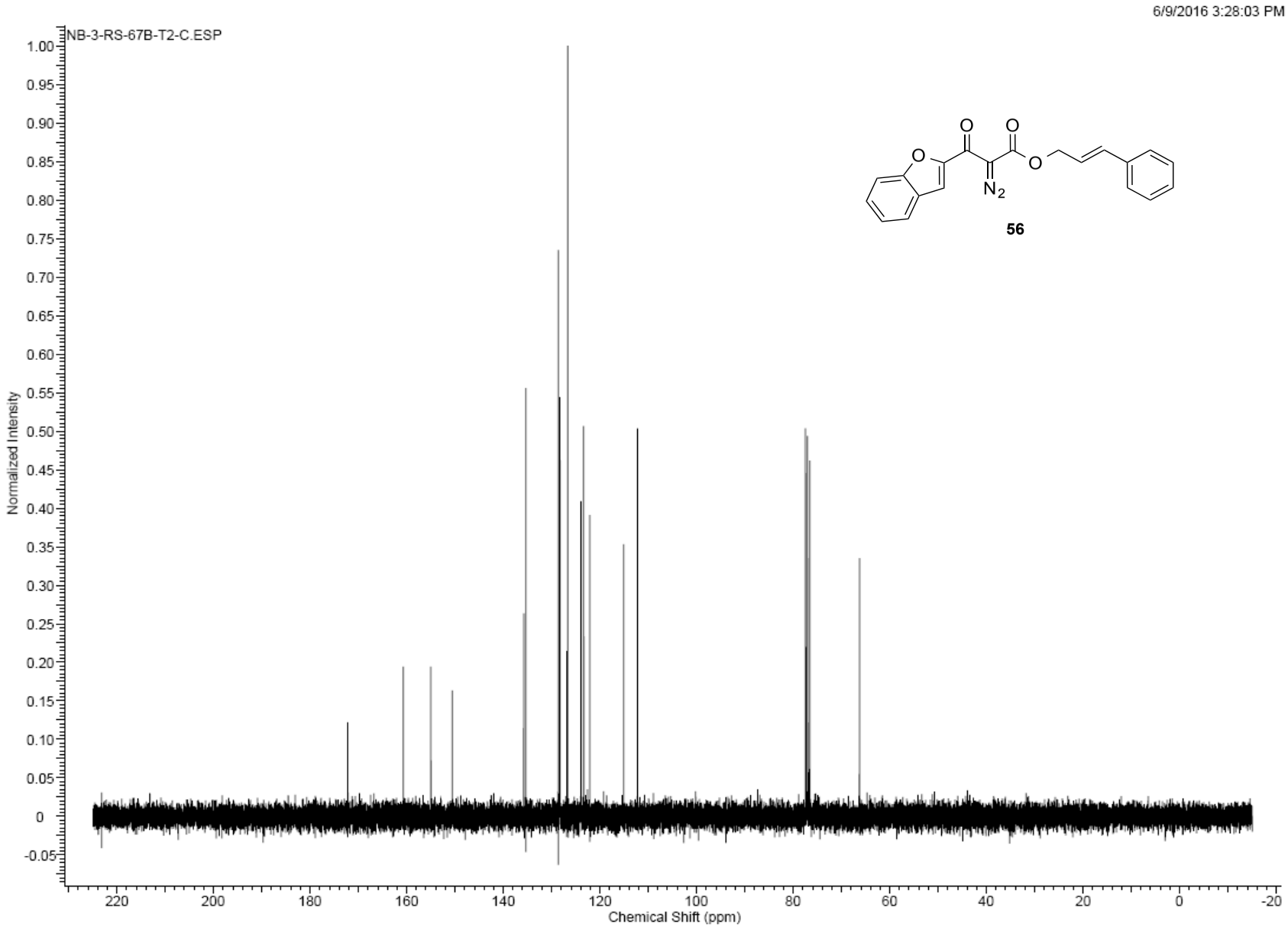
Synthesized according to the general procedure using **55** (70 mg, 0.22 mmol), and $In(OTf)_3$ (6.2 mg, 0.011 mmol) in DCM (1.1 mL). Purification carried out using preparative-TLC (eluting with EtOAc/hexane) to afford **54c** as an oily keto-enol mixture (34.3 mg, 49%)**.** **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.58 (s, 0.02H), 11.47 (s, 0.13H), 7.67 - 7.64 (m, 1.22H), 7.52 - 7.49 (m, 2.28H), 7.37 - 7.29 (m, 3.26H), 7.24 - 7.15 (m, 6.14H), 7.10 - 6.93 (m, 1.48H), 4.88 - 4.84 (m, 0.26H), 4.68 - 4.63 (m, 1H), 4.49 - 4.46 (m, 0.25H), 4.37 - 4.31 (m, 1H), 4.30 - 4.24 (m, 0.46H), 4.19 - 4.14 (m, 2H), 3.70 - 3.63 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 182.69, 171.49 (s, 2C), 155.82, 150.84 (s, 2C), 137.04 - 136.66 (m, 3C), 129.40 (s, 2C), 129.16 (s, 5C), 129.03 (s, 2C), 127.43 (s, 4C), 126.75, 124.16 (s, 3C), 123.58 (s, 2C), 112.43 (s, 4C), 79.24 (s, 3C), 69.73 (s, 2C), 51.23 (s, 3C), 45.49 (s, 2C).

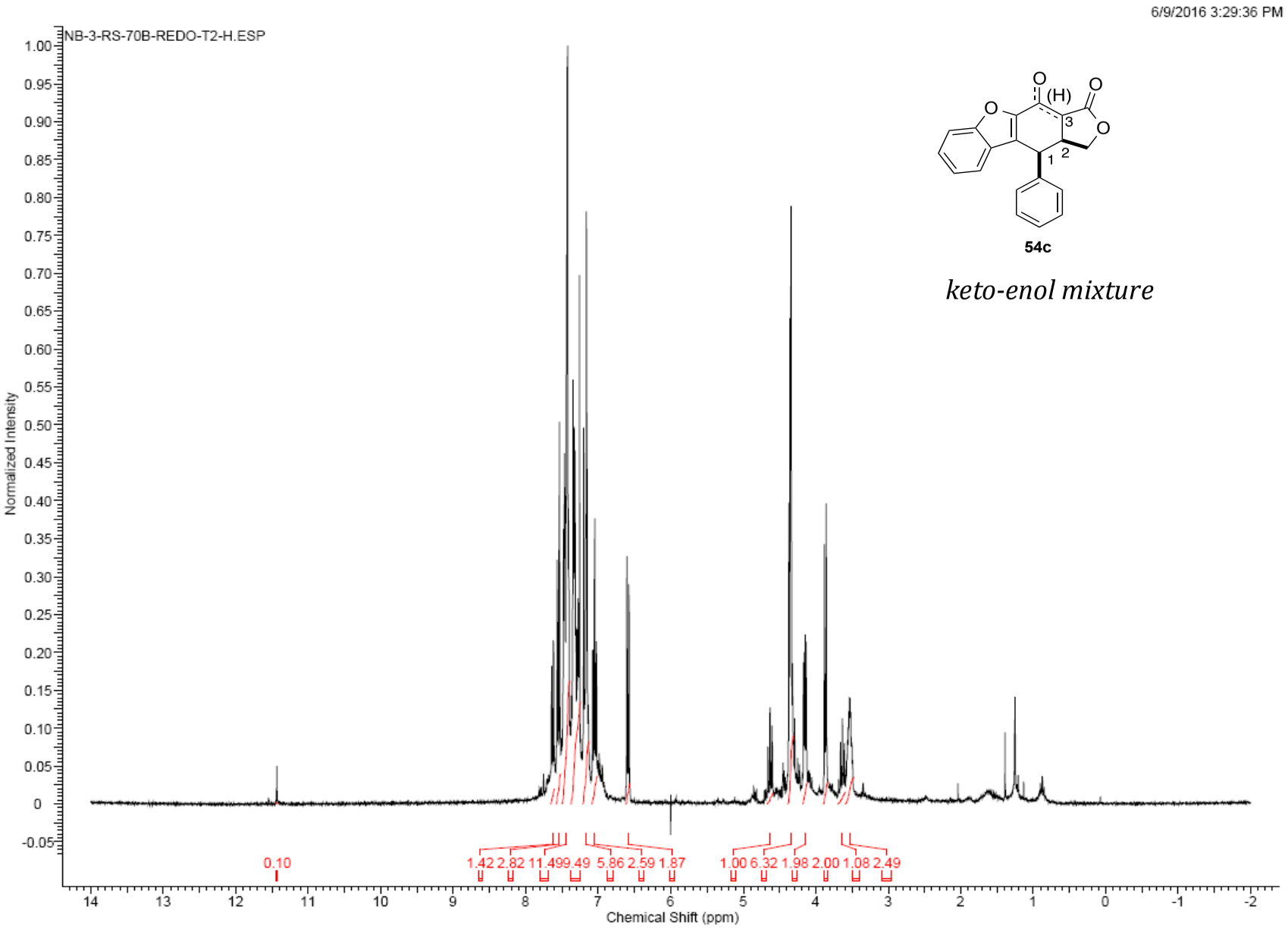
5.4.3.3 NMR Spectra



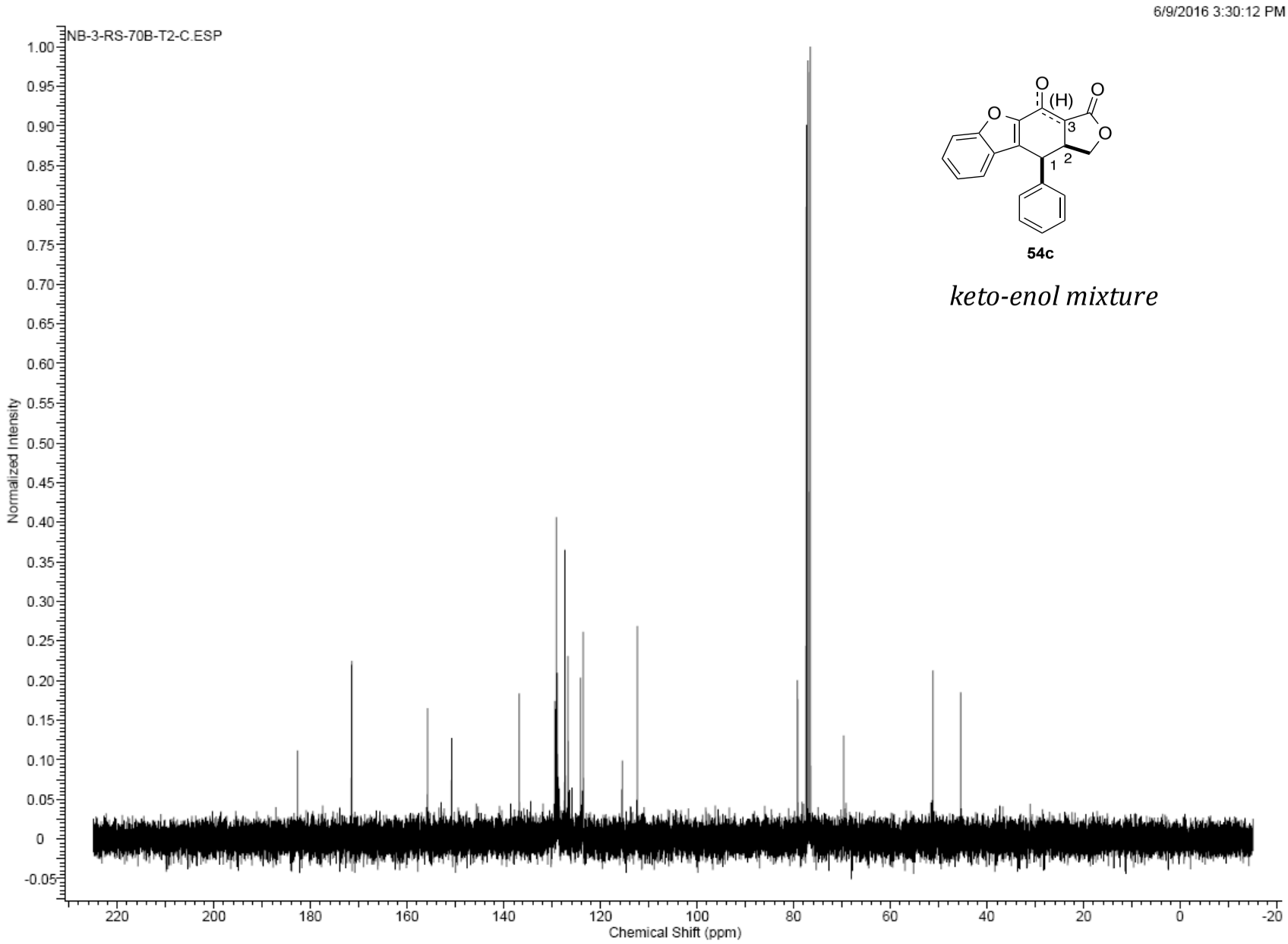

6/9/2016 3:25:56 PM
NB-3-RS-67A-T1.002.ESP
Normalized Intensity
Chemical Shift (ppm)
57
keto-enol mixture


6/9/2016 3:27:22 PM
NB-3-RS-67B-REDO-T2-H.ESP
Normalized Intensity
Chemical Shift (ppm)
0.94 1.04 1.07 1.14 6.06 1.11 1.22 2.00
O
O
O
O
N2
56


6/9/2016 3:28:03 PM
NB-3-RS-67B-T2-C.ESP
Normalized Intensity
Chemical Shift (ppm)
56



keto-enol mixture


6/9/2016 3:30:12 PM
NB-3-RS-70B-T2-C.ESP
Normalized Intensity
Chemical Shift (ppm)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
-0.05
220
200
180
160
140
120
100
80
60
40
20
0
-20
O
(H)
O
O
O
3
2
1
54c
keto-enol mixture

5.5 REFERENCES

1. (a) Reissig, H.-U.; Zimmer, R., Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003,** *103* (4), 1151-1196; (b) Schneider, T. F.; Werz, D. B., Ring-Enlargement Reactions of Donor−Acceptor-Substituted Cyclopropanes: Which Combinations are Most Efficient? *Org. Lett.* **2011,** *13* (7), 1848-1851.

2. (a) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J., Catalytic Formal Homo-Nazarov Cyclization. *Org. Lett.* **2009,** *11* (4), 1023-1026; (b) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J., Formal Homo-Nazarov and Other Cyclization Reactions of Activated Cyclopropanes. *Chem. Eur. J.* **2011,** *17* (51), 14527-14538; (c) Murphy, W. S.; Wattanasin, S., A new cyclisation involving cyclopropyl ketones. A short route to 1-aryltetralones. *Tetrahedron Lett.* **1980,** *21* (19), 1887-1890; (d) Cavitt, M. A.; Phun, L. H.; France, S., Intramolecular donor-acceptor cyclopropane ring-opening cyclizations. *Chem. Soc. Rev.* **2014,** *43* (3), 804-818.

3. (a) Yu, M.; Pagenkopf, B. L., Formal [3 + 2] Cycloadditions of Donor−Acceptor Cyclopropanes and Nitriles. *J. Am. Chem. Soc.* **2003,** *125* (27), 8122-8123; (b) Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y., Highly Diastereoselective Construction of Fused Carbocycles from Cyclopropane-1,1-dicarboxylates and Cyclic Enol Silyl Ethers: Scope, Mechanism, and Origin of Diastereoselectivity. *Chem. Eur. J.* **2012,** *18* (8), 2196-2201; (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S., Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate Ion Pair Pathway. *J. Am. Chem. Soc.* **2008,** *130* (27), 8642-8650; (d) Pohlhaus, P. D.; Johnson, J. S., Enantiospecific Sn (II)-and Sn (IV)-catalyzed cycloadditions of aldehydes and donor-acceptor cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (46), 16014-16015; (e) Pohlhaus, P. D.; Johnson, J. S., Enantiospecific Sn(II)- and Sn(IV)-Catalyzed

Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (46), 16014-16015.

4. (a) Lifchits, O.; Charette, A. B., A Mild Procedure for the Lewis Acid-Catalyzed Ring-Opening of Activated Cyclopropanes with Amine Nucleophiles. *Org. Lett.* **2008,** *10* (13), 2809-2812; (b) Wales, S. M.; Walker, M. M.; Johnson, J. S., Asymmetric Synthesis of Indole Homo-Michael Adducts via Dynamic Kinetic Friedel–Crafts Alkylation with Cyclopropanes. *Org. Lett.* **2013,** *15* (10), 2558-2561.

5. (a) Schneider, T. F.; Kaschel, J.; Werz, D. B., A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2014,** *53* (22), 5504-5523; (b) Braun, C. M.; Congdon, E. A.; Nolin, K. A., Diastereoselective 1,3-Dipolar Cycloaddition of Nitrones to Donor–Acceptor Cyclopropanes Catalyzed by a Calcium(II) Complex. *J. Org. Chem.* **2015,** *80* (3), 1979-1984; (c) Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P., Lewis Acid/Rhodium-Catalyzed Formal [3 + 3]-Cycloaddition of Enoldiazoacetates with Donor–Acceptor Cyclopropanes. *Org. Lett.* **2015,** *17* (14), 3568-3571; (d) Fang, J.; Hu, B.; Ren, J.; Wang, Z. W., Sc $(OTf)_3$-Catalyzed Tandem [3+ 2] Cycloaddition/Nucleophilic Ring-Opening Reaction of Cyclopropane 1, 1-Diesters with Azomethine Ylides. *Asian J. Chem.* **2011,** *23* (4), 1479; (e) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Y., (3 + 3)-Cyclodimerization of Donor–Acceptor Cyclopropanes. Three Routes to Six-Membered Rings. *J. Org. Chem.* **2011,** *76* (21), 8852-8868; (f) Sibi, M. P.; Ma, Z.; Jasperse, C. P., Enantioselective Addition of Nitrones to Activated Cyclopropanes. *J. Am. Chem. Soc.* **2005,** *127* (16), 5764-5765; (g) Young, I. S.; Kerr, M. A., Three-Component Homo 3 + 2 Dipolar Cycloaddition. A Diversity-Oriented Synthesis of Tetrahydro-1,2-oxazines and FR900482 Skeletal Congeners. *Org. Lett.* **2004,** *6* (1), 139-141; (h) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F., TiCl4 Promoted Formal [3 + 3] Cycloaddition of Cyclopropane 1,1-Diesters with Azides: Synthesis of Highly Functionalized Triazinines and Azetidines. *Org. Lett.* **2014,** *16* (18), 4896-4899.

6. Stork, G.; Marx, M., Six-membered rings via olefin participation in the opening of acylcyclopropanes. *J. Am. Chem. Soc.* **1969,** *91* (9), 2371-2373.

7. Corey, E. J.; Balanson, R. D., A simple synthesis of (±)-cedrene and (±)-cedrol using a synchronous double annulation process. *Tetrahedron Lett.* **1973,** *14* (34), 3153-3156.

8. Marino, J. P.; Long, J. K., New strategies for annulations: a highly convergent and stereoselective synthesis of an octahydronaphthalene synthon for dihydrocompactin. *J. Am. Chem. Soc.* **1988,** *110* (23), 7916-7917.

9. Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M., Total Synthesis of Prostaglandins F2α and E2 as the Naturally Occuring Forms. *J. Am. Chem. Soc.* **1970,** *92* (2), 397-398.

10. (a) Di Grandi, M. J., Nazarov-like cyclization reactions. *Org. Biomol. Chem.* **2014,** *12* (29), 5331-5345; (b) De Simone, F.; Waser, J., Cyclization of Cyclopropyl Carbonyls and the Homo-Nazarov Reaction. *CHIMIA* **2009,** *63* (3), 162-167.

11. Martin, M. C.; Shenje, R.; France, S., The Catalytic, Formal Homo-Nazarov Cyclization as a Template for Diversity-Oriented Synthesis. *Isr. J. Chem.* **2016**, n/a-n/a.

12. (a) Patil, D. V.; Cavitt, M. A.; France, S., Diastereoselective Synthesis of (±)-Deethyleburnamonine Using A Catalytic Cyclopropane Ring-Opening/Friedel-Crafts Alkylation Strategy (Dedicated to Dr. Albert Padwa on his 75th birthday). *Heterocycles* **2012,** *84* (2), 1363-1373; (b) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S., An efficient synthesis of hydropyrido[1,2-*a*]indole-6(7H)-ones via an In(III)-catalyzed tandem cyclopropane ring-opening/Friedel-Crafts alkylation sequence. *Chem. Commun.* **2011,** *47* (37), 10278-10280; (c) Patil, D. V.; Phun, L. H.; France, S., Indium-Catalyzed Homo-Nazarov Cyclizations of Alkenyl Cyclopropyl Ketones. *Org. Lett.* **2010,** *12* (24), 5684-5687; (d) Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S., A Catalytic Homo-Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones. *Org. Lett.* **2011,** *13* (8), 1952-1955; (e) Yadav, V. K.; Kumar, N. V.,

2,3-Heteroaromatic ring-fused cyclohexanonesvia heteroaromatic homo-Nazarov cyclization of donor-acceptor substituted cyclopropanes. *Chem. Commun.* **2008,** (32), 3774-3776; (f) Yadav, V. K.; Naganaboina, V. K.; Hulikal, V., Allylsilane-interrupted homo-Nazarov cyclization and synthesis of bicyclo[3.2.1]octan-8-ones. *Tetrahedron Lett.* **2014,** *55* (12), 2015-2018; (g) Aponte-Guzmán, J.; Taylor, J. E.; Tillman, E.; France, S., Catalytic, Formal Homo-Nazarov-Type Cyclizations of Alkylidene Cyclopropane-1,1-Ketoesters: Access to Functionalized Arenes and Heteroaromatics. *Org. Lett.* **2014,** *16* (14), 3788-3791; (h) Shenje, R.; Williams, C. W.; Francois, K. M.; France, S., Catalysis and Chemodivergence in the Interrupted, Formal Homo-Nazarov Cyclization Using Allylsilanes. *Org. Lett.* **2014,** *16* (24), 6468-6471.

13. Shenje, R.; Martin, M. C.; France, S., A Catalytic Diastereoselective Formal [5+2] Cycloaddition Approach to Azepino[1,2-*a*]indoles: Putative Donor–Acceptor Cyclobutanes as Reactive Intermediates. *Angew. Chem. Int. Ed.* **2014,** *53* (50), 13907-13911.

14. De Simone, F.; Gertsch, J.; Waser, J., Catalytic Selective Cyclizations of Aminocyclopropanes: Formal Synthesis of Aspidospermidine and Total Synthesis of Goniomitine. *Angew. Chem. Int. Ed.* **2010,** *49* (33), 5767-5770.

15. Wenkert, E.; Hudlicky, T., Synthesis of eburnamonine and dehydroaspidospermidine. *J. Org. Chem.* **1988,** *53* (9), 1953-1957.

16. (a) Stoit, A. R.; Pandit, U. K., Models of folate cofactors 20. an approach to deethyleburnamonine. *Tetrahedron* **1989,** *45* (3), 849-854; (b) Lounasmaa, M.; Belle, D. D.; Tolvanen, A., Total synthesis of (±)-deethyleburnamonine and vindeburnol (RU 24722) with the corresponding nitriles as starting material. *Heterocycles* **1999,** *5* (51), 1125-1130; (c) Castaigne, A., Process for the preparation of deethyleburnamonines. Google Patents: **1974**.

17. (a) Jones, B. T.; Avetta, C. T.; Thomson, R. J., Total synthesis of propolisbenzofuran B. *Chem. Sci.* **2014,** *5* (5), 1794-1798; (b) Banskota, A. H.; Tezuka,

Y.; Midorikawa, K.; Matsushige, K.; Kadota, S., Two novel cytotoxic benzofuran derivatives from Brazilian propolis. *J. Nat. Prod.* **2000,** *63* (9), 1277-1279.

CHAPTER 6 CONCLUSIONS AND FUTURE OUTLOOK

6.1 Introduction: Strained Carbocycles As Precursors To Molecular Complexity

Cyclopropanes and cyclobutanes, when activated with donor and acceptor groups, provide facile access to a plethora of interesting chemical scaffolds. Importantly, D-A cyclopropanes and cyclobutanes undergo efficient reactivity under mild Lewis acid conditions. This reactivity can be carried out in a modular fashion allowing for broad substrate scope enabling access to wider chemical space. In this thesis, D-A cyclopropanes and cyclobutanes were systematically used as chemical precursors to a variety of natural product-like scaffolds. Firstly, novel interrupted formal homo-Nazarov cyclizations were investigated and provided concise entry into α-arylated cyclohexenols, α-allylated cyclohexenols, and hexahydrobenzofurans (Figure 6.1). In a different pursuit, formal [5+2] cycloadditions, presumably occurring via D-A cyclobutane intermediates, afforded efficient, high-yielding and diastereoselective access to azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles, two important backbones in the indole alkaloid family of natural products (Figure 6.1). Finally, homo-Nazarov-inspired cyclizations of strategically-chosen D-A cyclopropanes were successfully employed in the synthesis of hydropyrido[1,2-*a*]indoles (under continuous flow conditions) as well the dihydrodibenzo[*b*,*d*]furan core (featured in natural product propolisbenzofuran B) (Figure 6.1).

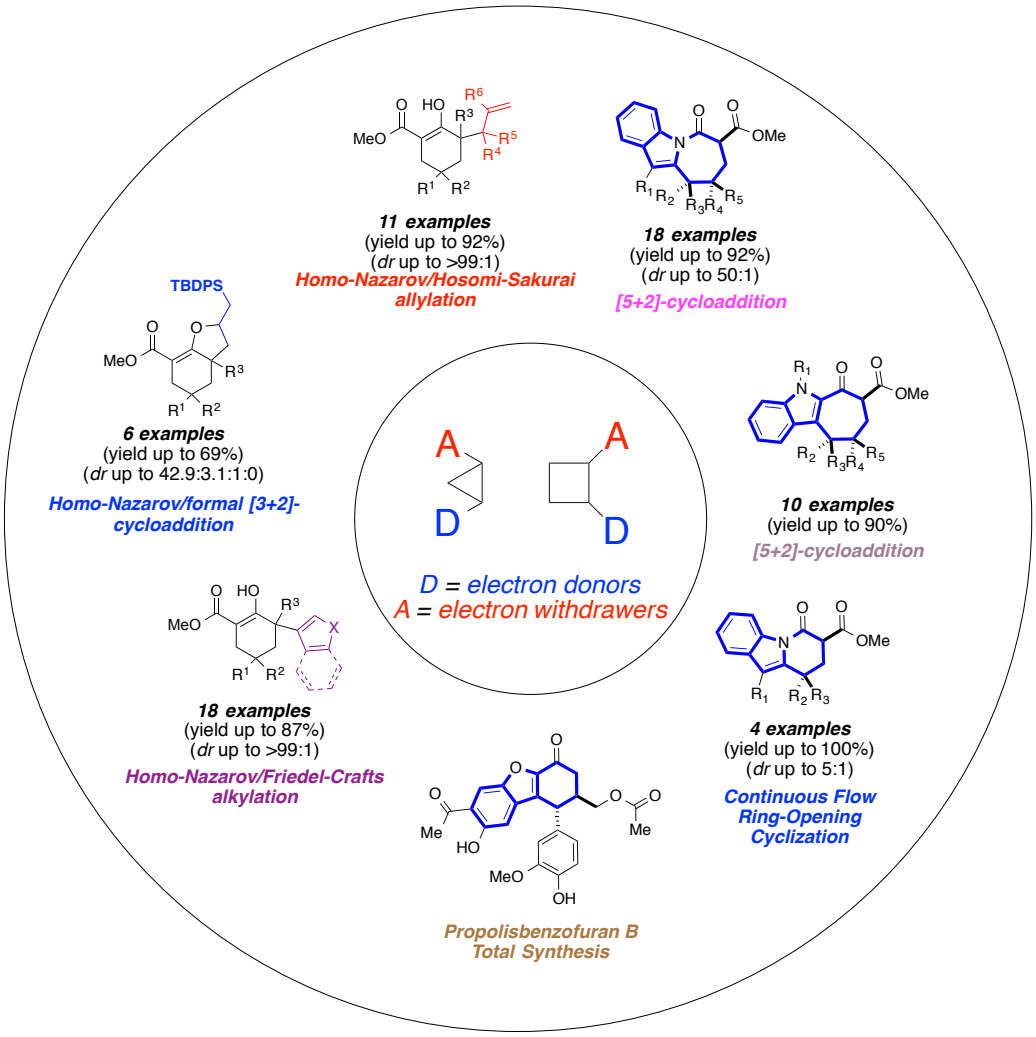


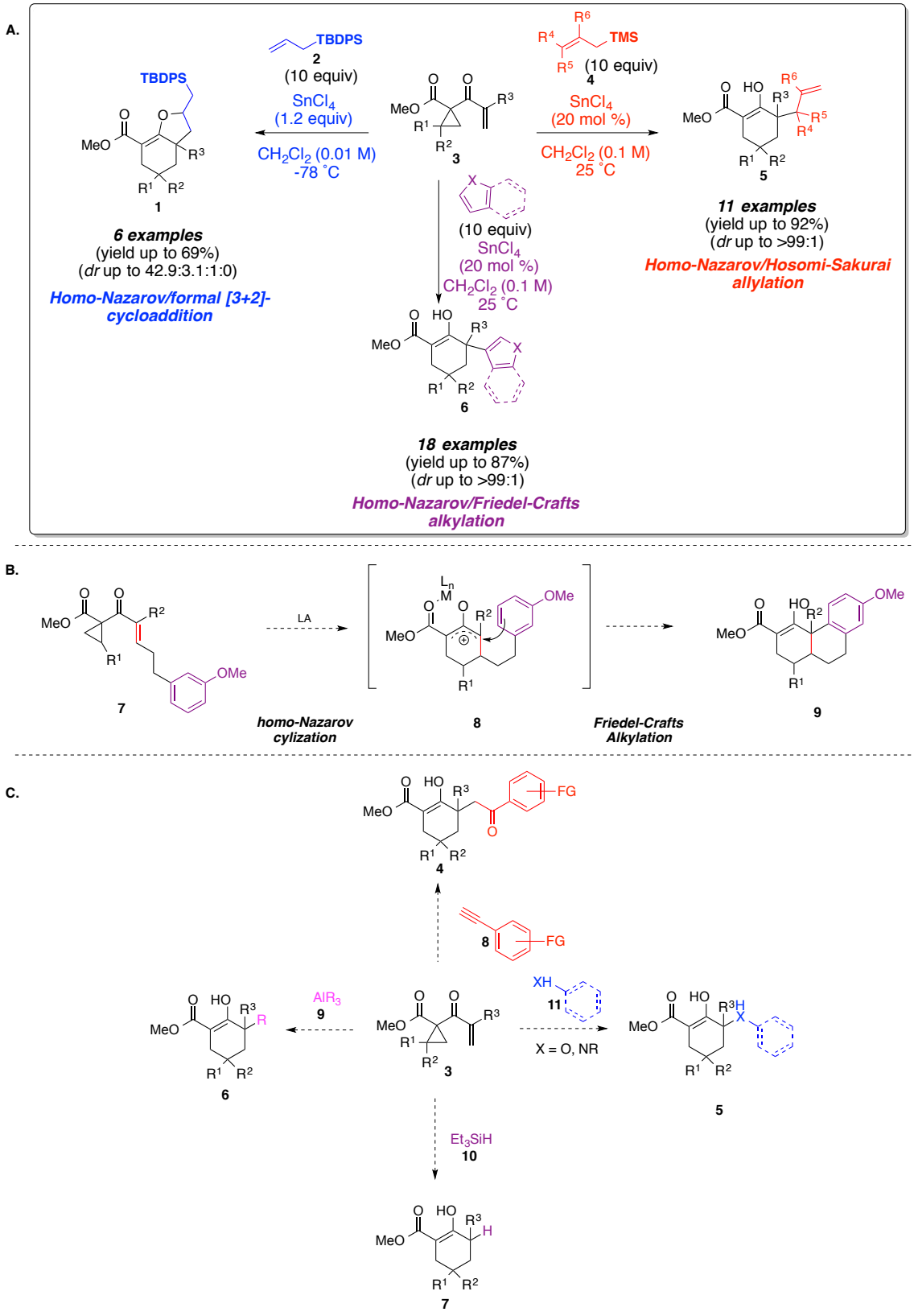
Figure 6.1. Chemical Diversity Acheived Through Strained Carbocycles.

Presumably, the successful application of D-A cyclopropanes and cyclobutanes for enabling rapid chemical diversity and molecular complexity will alert the synthetic community about the potential of homo-Nazarov and homo-Nazarov-inspired reactions as tools for chemical synthesis. The knowledge gained from the reactivity of D-A cyclopropanes and cyclobutanes in this thesis opens up many avenues of research areas whose exploration could lead to effective expansion of chemical space.

6.2 Other Potential Interrupted Homo-Nazarov Cyclizations

Chapter 2 highlighted novel, Lewis acid-mediated interrupted homo-Nazarov cyclizations using D-A cyclopropanes, of the type **3**, for the synthesis of hexahydrobenzofurans **1**, arylated cyclohexenols **6** allylated cyclohexenols **5** (Scheme 6.1, A). In these methodologies, allylsilanes and electron-rich (hetero)aromatics were used as nucleophiles for the interception of the oxyallyl cations formed following ring-opening cyclization. In addition to performing these syntheses under mild Lewis acid conditions, much effort was dedicated to expanding the substrate scope; a variety of cyclopropanes, allylsilanes, and (hetero)aromatics were utilized, in a modular fashion, leading to robust methodologies.

As an extension of this chemistry, other synthetic variations can be envisioned. Firstly, modification of the D-A cyclopropane precursors to possess a nucleophilic tether, such as in **7**, would conceivably enable a rapid intramolecular oxyallyl cation trapping (depicted in **8**) (Scheme 6.1, B). Such reactivity would lead to tricycles, of the type **9**, in a single synthetic step, and would demonstrate the potential of the homo-Nazarov cyclization as a synthetic tool for rapid generation of molecular complexity. Other potential interrupted homo-Nazarov reactivity could be done in an intermolecular fashion using nucleophiles such alkynes **8**, heteroatoms **11**, hydride transfer agents such as **10**, and alkyl aluminum reagents of the type **9** (Scheme 6.1, C). Synthetic transformations with these reagents would lead to a divergent plethora of chemical scaffolds from the same precursor cyclopropanes.



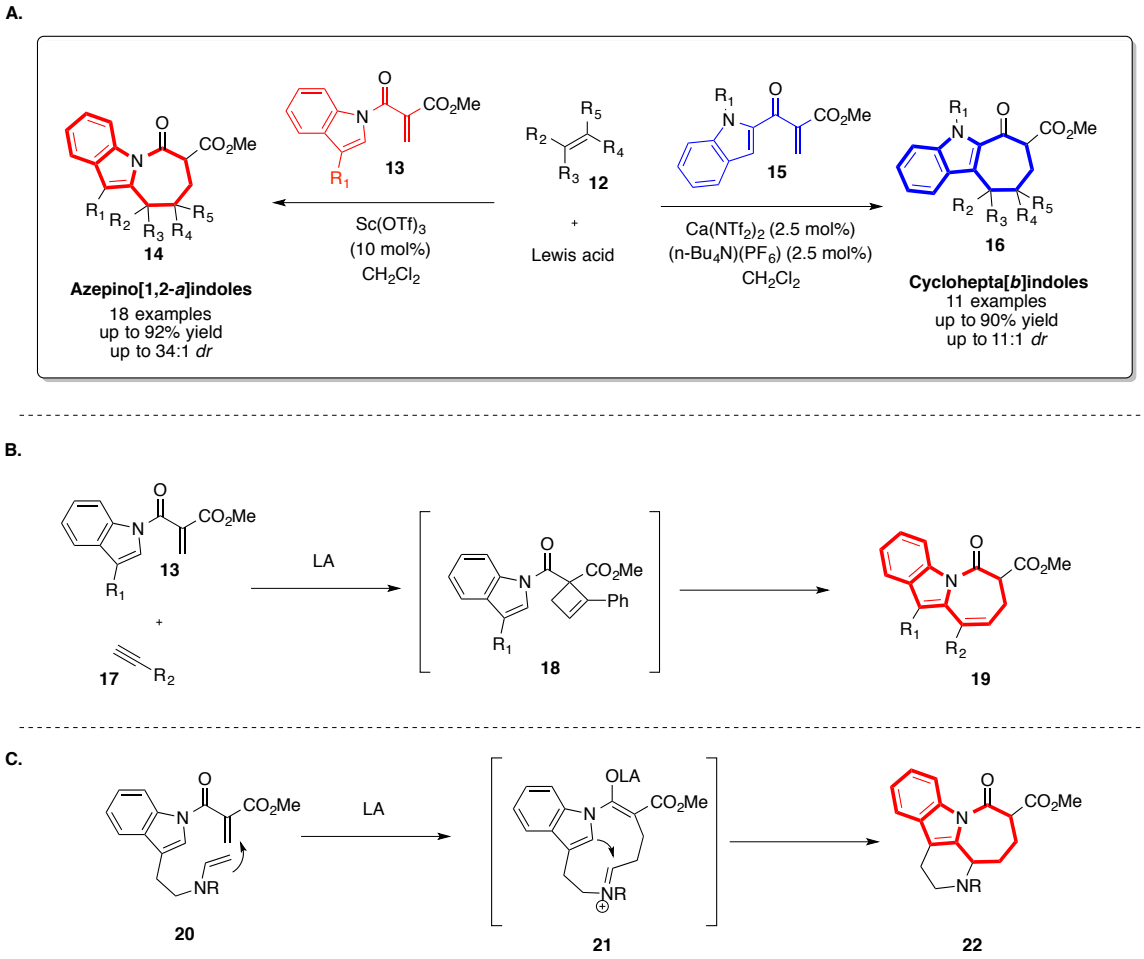
Scheme 6.1. Plausible Interrupted Homo-Nazarov Cyclizations.

6.3 Possibilities with Formal [5+2]-Cycloadditions

Chapter 3 explored new formal [5+2]-cycloadditions using indole-based alkylidenes **13** and **15** for accessing azepino[1,2-*a*]indoles **14** and cyclohepta[*b*]indoles **16** respectively (Scheme 6.2, A). These methods, involving Lewis acid-catalysis, were thought to proceed via intermediate D-A cyclobutanes that rapidly cycloisomerized to the final 7-membered products in a final, irreversible transformation. The scope of these methodologies proved particularly broad, variously-substituted alkylidenes and alkenes were well-tolerated. Furthermore, for the synthesis of azepino[1,2-*a*]indoles, in particular, products were formed in high degrees of diastereoselection (up to 34:1).

In light of the results obtained in Chapter 3, formal [5+2]-cycloadditions involving alkynes **17** can be envisioned (Scheme 6.2, B). Conceivably, reactivity with these substrates would initially afford D-A cyclobutenes **18**, intermediates that would likely ring-open and cyclize to corresponding azepino **19** (bearing unsaturation on the 7-membered ring). Development of a methodology of this type would be beneficial to the synthetic community; no reports of D-A cyclobutene ring-opening cyclization exist in literature.

In another variant of this methodology, intramolecular formal [5+2]-cycloadditions of tethered alkylidenes **20** under Lewis acid conditions could provide iminium intermediate **21** (Scheme 6.2, C). A subsequent intramolecular π-attack onto the iminium would afford tetracycle **22**. Nitrogen-substituted tetracycles, such as **22**, are an important scaffold found in many indole alkaloid natural products and their synthesis proved particularly elusive using the intermolecular approach developed in Chapter 3.



Scheme 6.2. Possibilities with Formal [5+2]-Cycloadditions.

Due to our continued interest in indole alkaloid natural products, most of the [5+2]-cycloaddition reactivity explored involved *N*-acyl indole-based alkylidenes (of the type **13** and **15**) for the synthesis of azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles. Conceivably, this reactivity can be easily translated to other scaffolds as well, and this would allow entry into: (1) pyrrolo[1,2-*a*]azepinones (**23**); cyclohepta[*b*]pyrroles (**24**); cyclohepta[*b*]furans (**25**); and benzo-fused cycloheptenones (**26**) (Figure 6.2). These potential scaffolds indicate the enormous synthetic potential of [5+2]-cycloadditions as well as D-A cyclobutane reactivity.

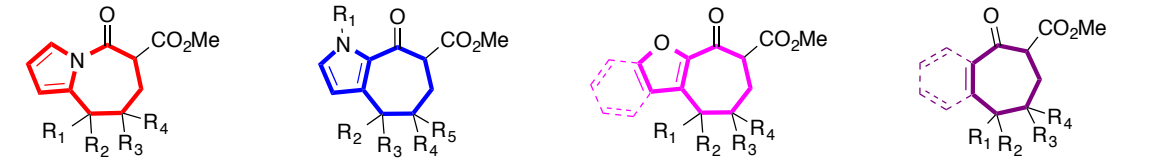


Figure 6.2. Potential Scaffolds via Formal [5+2]-Cycloadditions.

6.4 Conclusion

Highlighted in this thesis were a few novel methodologies pioneered to date. Methods were developed, for the benefit of the synthetic community, to enable access to the following: azepino[1,2-*a*]indoles, cyclohepta[*b*]indoles, functionalized cyclohexenols, hexahydrobenzofurans, and contiguous, tetracyclic heteroaromatic scaffolds. In pursuing these scaffolds, completely new reactivity, was unfolded which included: (1) ring-opening cyclizations of D-A cyclobutanes; and (2) cycloisomerizations of dense, lactone-fused D-A cyclopropanes. Additionally, a strategy for an unprecedented bi-catalytic, tandem continuous flow approach to hydropyrido[1,2-*a*]indoles successfully forged using "green", scalable, and high-yielding conditions. Throughout this thesis, significant effort was dedicated to widening the accessible chemical space by developing synthetic strategies with particular emphasis on modularity and breath of scope. Presumably, with these methods in hand, synthetic chemists can now apply them, directly, towards the synthesis of select natural products and pharmaceutically relevant compounds.